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Effect of *Quinapril* on Intimal Hyperplasia After Coronary Stenting as Assessed by Intravascular Ultrasound

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Angiotensin-converting enzyme (ACE) inhibitors have been experimentally shown to prevent restenosis after balloon injury.[1] However, randomized trials with ACE inhibitors, such as cilazapril[2,3] and fosinopril,[4] have failed to demonstrate the effect of ACE inhibition on the occurrence of angiographic restenosis after conventional balloon angioplasty. The present study was designed to test whether quinapril can prevent lumen loss after coronary angioplasty followed by stent implantation. Quinapril is an ACE inhibitor characterized by a short accumulation half-life and potent binding affinity for plasma and tissue ACEs.[5] In addition, the mechanism by which restenosis occurs after coronary artery intervention may differ between conventional balloon angioplasty and stent implantation.[6] In-stent restenosis results predominantly from neointimal hyperplasia, consisting of smooth muscle cell migration and extracellular matrix formation,[7,8] not from late recoil.[6] In this prospective study, we analyzed the lumen loss of the in-stent area using quantitative planar and volumetric intravascular ultrasound (IVUS) analysis as well as quantitative coronary angiography (QCA) in 100 patients who underwent successful coronary stent implantation.

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From September 1996 to December 1997, 100 consecutive patients underwent successful implantation of a Palmaz-Schatz stent (Cordis, Johnson & Johnson Interventional Systems, Miami, Florida) in Ogaki Municipal Hospital. All patients had functionally significant narrowing in the major coronary arteries, as demonstrated angiographically, and had received elective balloon angioplasty followed by coronary stenting aiming for an "optimal" result. Patients with renal or liver diseases by standard laboratory screen or unsatisfactory stent implantation were excluded from the study. All the patients were prospectively asked to undergo a systematic 6-month angiographic follow-up. Patients were randomly assigned to quinapril treatment (10 mg or 20 mg of quinapril daily; average dose of 18 mg/day) or to a control group after stent implantation. No placebo tablets were administered in the control group. The aims of the study were explained to each patient and informed consent was obtained before the intervention procedure. The trial was performed according to Declaration of Helsinki protocols.

Treatment with 200 mg ticlopidine and 81 mg aspirin daily started several days before the procedure and continued until the time of follow-up. Balloon dilation was performed according to conventional technique. A coronary arteriogram was obtained before balloon angioplasty, after stent implantation, and at 6-month follow-up after the administration of 0.2 mg intracoronary nitroglycerin. If the patient required revascularization of the target lesion earlier, angioplasty was performed at that time. These results were used as the 6-month results. All films were analyzed independently by 2 core angiographic laboratories blinded to the treatment assignment. Reference lumen diameter and minimal lumen diameter were determined on end-diastolic frame by a computer-assisted, edge-detection algorithm using an off-line system (QCA-CMS System; MEDIS, Inc., Leiden, the Netherlands). At 6 months postoperatively, follow-up angiography was performed at the same projections as used for the baseline study. With the outer diameter of the contrast-filled catheter used as a reference for calibration, the minimal lumen diameter from the "worst" view was recorded. The reference was averaged from 10-mm-long angiographically normal segments proximal and distal to the lesion; when a normal proximal segment could not be identified, only a distal segment was analyzed. To define restenosis, we used a categorical approach with the criterion of ≥50% diameter narrowing within the stent and in the segment, including the stent plus its edges (within 5 mm) at follow-up.

In addition, 2 independent laboratories blinded to the treatment analyzed the recorded videotape after intervention and at follow-up. The system (Cardiovascular Imaging Systems, Inc., Boston, Massachusetts) incorporated a 30-MHz beveled transducer mounted on the end of a flexible shaft that rotated at 1800 rpm within a 3.2Fr imaging sheath (Ultra Cross TM 3.2; Boston Scientific SCIMED, Natick, Massachusetts). All studies were recorded during transducer pullback on a high resolution super-VHS tape for off-line analysis at a pull-back speed of 0.5 mm/s. Based on these image slices, the stent and lumen cross-sectional area were traced manually using computerized planimetry,

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and stent and lumen volumes were calculated using Simpson's rule.[9] The cross-sectional area of intimal hyperplasia present within the stent was calculated as the stent cross-sectional area minus the lumen cross-sectional area. The reference lumen cross-sectional areas were the lumen areas at the most visually normal anatomic cross sections within 10 mm proximal and distal to the stent, but before any major side branches.

Smoking history was obtained during subject interviews. Subjects with a history of taking medication for hypertension or those whose average blood pressure was ≥90 mm Hg in diastole and/or ≥140 mm Hg in systole by ≥2 measurements were considered hypertensive. Diabetes mellitus was diagnosed by the criteria of the American Diabetes Association of 1997.[10] Body mass index was calculated as weight divided by height squared (kilograms per square meter). Fasting blood samples were collected for plasma lipid concentrations. Hypercholesterolemia and hypertriglyceridemia were defined as >220 and >150 mg/dl, respectively.

The results are expressed as the mean ± SD. Data were collected and stored in an Apple computer (Apple Japan, Inc., Tokyo, Japan) using StatView 5.0 software (SAS Institute, Inc., Cary, North Carolina). When appropriate, the unpaired Student's *t* test or chi-square test was used to compare the differences between the 2 groups. A p value of <0.05 was considered statistically significant.

Among the 50 patients in the quinapril group, 1 dropped out of the study after developing a severe cough as an adverse effect of treatment. Thus, the angiographic follow-up was performed in 50 control group (100%) and 49 quinapril group (98%) patients. There was no difference in the prevalence of risk factors and baseline angiographic characteristics between the control and quinapril groups (Table 1). Despite a lack of difference in the reference diameter between the 2 groups, the minimal lumen diameters were higher and percent diameter stenoses were lower in the quinapril group than in the controls at 6-month follow-up (Table 2); this difference, however, did not reach statistical significance.

Although IVUS-guided coronary angioplasty was performed in all subjects, IVUS measurements both after stent implantation and at the 6-month follow-up were available for only 36 controls and 31 patients treated with quinapril. In some of the remaining cases, IVUS imaging was not made due to an extreme decrease in lumen area, which prevented the passage of a probe through the stent. In addition, because follow-up study was performed using a 6Fr guiding catheter through a right brachial approach, there were technical limitations. There were no differences between the reference cross-sectional area after intervention and that at follow-up (Table 3). However, despite this lack of difference after intervention, the reduction of the minimal lumen cross-sectional area was inhibited by quinapril treatment ($p = 0.029$). The percent area stenosis calculated from the minimal and reference lumen cross-sectional areas was also improved by quinapril treatment ($p = 0.005$).

TABLE 1 Baseline Clinical and Angiographic Characteristics Assigned to Angiotensin-Converting Enzyme Inhibitor Therapy

Variable	Control Group (n = 50)	Quinapril Group (n = 49)
Age (yrs)	63.7 ± 8.7	65.9 ± 9.2
Men/women	38/12	39/10
Body mass index (kg/m²)	24 ± 3	23 ± 3
Cigarette smoking	14 (36%)	19 (30%)
Systemic hypertension	15 (35%)	17 (32%)
Diabetes mellitus	12 (38%)	9 (40%)
Hypercholesterolemia	11 (39%)	10 (39%)
Hypertriglyceridemia	14 (36%)	17 (32%)
Recent MI/OMI/non-MI	23/8/15	31/7/8
Coronary lesion		
Left anterior descending	24 (48%)	25 (51%)
Left circumflex	5 (10%)	10 (20%)
Right coronary artery	21 (42%)	14 (29%)
ACC/AHA lesion type		
A	7 (14%)	6 (12%)
B1	17 (34%)	15 (31%)
B2	16 (32%)	14 (29%)
C	10 (20%)	14 (29%)
Moderate or severe calcification	7 (14%)	3 (6%)
Eccentric lesion	28 (56%)	21 (43%)
Ostial lesion	2 (4%)	4 (8%)

Results are given as mean ± SD. Hypercholesterolemia, total cholesterol >220 mg/dl. Hypertriglyceridemia, triglycerides >150 mg/dl. There were no significant differences between the 2 groups by Student's *t* test or chi-square test.

ACC = American College of Cardiology; AHA = American Heart Association; MI = myocardial infarction; OMI = old myocardial infarction.

TABLE 2 Quantitative Coronary Angiographic Results Assigned to Angiotensin-Converting Enzyme Inhibitor Therapy

Variable	Control Group (n = 50)	Quinapril Group (n = 49)
Reference (mm)		
Before intervention	3.00 ± 0.47	3.08 ± 0.57
After intervention	3.03 ± 0.40	3.10 ± 0.59
Follow-up	2.99 ± 0.44	3.02 ± 0.51
Minimal lumen diameter (mm)		
Before intervention	0.59 ± 0.41	0.62 ± 0.36
After intervention	3.26 ± 0.49	3.30 ± 0.48
Follow-up	1.86 ± 0.68	2.08 ± 0.81
Diameter stenosis (%)		
Before intervention	81.1 ± 12.8	80.0 ± 11.3
After intervention	−9.7 ± 11.9	−7.5 ± 12.8
Follow-up	37.9 ± 20.6	31.2 ± 23.0
Restenosis [n [%]]	12 (24)	6 (12)

Results are given as mean ± SD.

To determine whether or not there was any variation in QCA findings between subjects who underwent and those who did not undergo IVUS study, we compared the QCA results between these 2 groups (Table 4). The results showed that there was no difference between the QCA results of those who underwent and those who did not undergo IVUS study, indicating that a significant preventive effect of quinapril treatment on lumen loss in stented segments can be evaluated by IVUS study, but cannot be adequately evaluated by

TABLE 3 Quantitative Planar Intravascular Ultrasound Analysis Results Assigned to Angiotensin-Converting Enzyme Inhibitor Therapy

Variable	Control Group (n = 36)	Quinapril Group (n = 31)
Reference lumen cross-sectional area (mm²)		
After intervention	8.17 ± 1.96	7.85 ± 2.23
Follow-up	7.61 ± 2.09	7.48 ± 1.74
Minimal lumen cross-sectional area (mm²)		
After intervention	7.24 ± 1.37	7.07 ± 1.74
Follow-up	3.73 ± 1.39	4.48 ± 1.31*
Area stenosis (%)		
After intervention	10.2 ± 16.5	7.9 ± 20.3
Follow-up	50.4 ± 15.9	39.1 ± 15.9†

Results are given as mean ± SD.
*p <0.05; †p <0.01 versus controls.

TABLE 4 Quantitative Coronary Angiographic (QCA) Results Assigned to the Subjects With and Without Intravascular Ultrasound (IVUS) Study

	Control Group (n = 36)	Quinapril Group (n = 31)	p Value
QCA results from the subjects with IVUS study			
Minimal lumen diameter (mm)			
Follow-up	1.91 ± 0.71	2.11 ± 0.74	0.28
Diameter stenosis (%)			
Follow-up	37 ± 22	30 ± 23	0.23
Restenosis (+/−)	8/28 (14)	2/29 (18)	0.071
QCA results from the subjects without IVUS study			
Minimal lumen diameter (mm)			
Follow-up	1.79 ± 0.64	2.07 ± 0.95	0.34
Diameter stenosis (%)			
Follow-up	38 ± 18	32 ± 24	0.40
Restenosis (+/−)	4/10	4/14	0.68

QCA analysis. Volumetric IVUS analysis was performed for 35 controls and 31 patients treated with quinapril, because 1 control group subject did not have sufficient IVUS imaging for analysis. Although there was no difference in the lumen volume immediately after the intervention, lumen volume at follow-up was significantly greater in the quinapril than in the control group, resulting in a significant decrease in intimal hyperplasia (Table 5).

During the 6-month follow-up period, there was no difference in the incidence of clinical events such as death, acute myocardial infarction, coronary artery bypass grafting, and repeated angioplasty for in-stent restenosis (data not shown).

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The results of the IVUS analysis indicated that 6 months of therapy with quinapril attenuated the development of intimal hyperplasia, although no significantly favorable effects of quinapril treatment were

TABLE 5 Volumetric Intravascular Ultrasound Analysis Results Assigned to Angiotensin-Converting Enzyme Inhibitor Therapy

	Control Group (n = 35)	Quinapril Group (n = 31)	p Value
Lumen volume in stent (mm³/mm)			
After intervention	7.79 ± 1.25	7.81 ± 1.65	0.76
Follow-up	5.29 ± 1.59	6.04 ± 1.29	0.045
Intimal hyperplasia volume (mm³/mm)	2.53 ± 1.28	1.77 ± 1.11	0.014

Results are given as mean ± SD. Volumes are divided by stent length (mm).

apparent by QCA analysis. Quinapril has high tissue specificity for ACEs, and its dissociation from ACEs is markedly prolonged.[11] ACE inhibition through quinapril treatment has been shown to ameliorate endothelial dysfunction,[12] which may be one of the first steps in the development of atherosclerosis,[13] in patients with coronary artery disease.

In conclusion, the present study demonstrated that quinapril treatment reduced the decreases in the minimal lumen area and the lumen volume in stented segments and inhibited the development of intimal hyperplasia, based on IVUS analysis at 6-month follow-up after stent implantation. These results suggest that quinapril therapy favorably influences the lumen loss of in-stent dimensions.

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CLINICAL RESEARCH — Interventional Cardiology

A Novel Bioresorbable Polymer Paclitaxel-Eluting Stent for the Treatment of Single and Multivessel Coronary Disease

Primary Results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II Study

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Objectives The aim was to compare safety and effectiveness of the CoStar drug-eluting stent (DES) (Conor MedSystems, Menlo Park, California) with those of the Taxus DES (Boston Scientific, Maple Grove, Minnesota) in de novo single- and multivessel percutaneous coronary intervention (PCI).

Background Paclitaxel elution from a stent coated with biostable polymer (Taxus) reduces restenosis after PCI. The CoStar DES is a novel stent with laser-cut reservoirs containing bioresorbable polymer loaded to elute 10 μg paclitaxel/30 days.

Methods Patients undergoing PCI for a single target lesion per vessel in up to 3 native epicardial vessels were randomly assigned 2:2 to CoStar or Taxus. Primary end point was 8-month major adverse cardiac events (MACE), defined as adjudicated death, myocardial infarction (MI), or clinically driven target vessel revascularization (TVR). Protocol-specified 8-month angiographic follow-up included 457 vessels in 288 patients.

Results Of the 1,700 patients enrolled, 1,675 (98.5%) were evaluable (CoStar = 989; Taxus = 686), including 1,330 (79%) single-vessel and 345 (21%) multivessel PCI. The MACE rate at 8 months was 11.0% for CoStar versus 6.9% for Taxus ($p < 0.005$), including adjudicated death (0.5% vs. 0.7%, respectively), MI (3.4% vs. 2.4%, respectively), and TVR (8.1% vs. 4.3%, respectively). Per-vessel 8-month in-segment late loss was 0.49 mm with CoStar and 0.18 mm with Taxus ($p < 0.00001$). Findings were consistent across pre-specified subgroups.

Conclusions The CoStar DES is not noninferior to the Taxus DES based on per-patient clinical and per-vessel angiographic analyses. The relative benefit of Taxus is primarily attributable to reduction in TVR. Follow-up to 9 months showed no apparent difference in death, MI, or stent thrombosis rates. (J Am Coll Cardiol 2008;51:1543–52)

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April 22, 2008:1543–52

Abbreviations and Acronyms

CEC = clinical events committee
DES = drug-eluting stent(s)
ECG = electrocardiography/electrocardiogram
FDA = Food and Drug Administration
IVUS = intravascular ultrasound
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PLGA = poly-lactic-co-glycolic acid
QCA = quantitative coronary angiography
TVR = target vessel revascularization

Currently available drug-eluting stents (DES) reduce restenosis by inhibiting fibromuscular hyperplasia through targeted delivery of cytostatic drugs, such as sirolimus or paclitaxel, from surface coatings using durable polymers (1,2). Concerns with such first generation DES include infrequent but catastrophic late stent thrombosis (3–5). Although the cause of late stent thrombosis is likely multifactorial, durable polymer surface coatings may play a role (6–8).

The CoStar (Conor MedSystems, Menlo Park, California) stent is a novel cobalt chromium alloy DES platform designed to elute paclitaxel without the use of a surface polymer coating via multiple laser-cut reservoirs within the stent struts, which are filled with a bioresorbable poly–lactic-co-glycolic acid (PLGA) polymer. After drug delivery and subsequent complete polymer bioresorption, only the biologically inert bare-metal platform remains (Fig. 1). Reduction of tissue exposure to polymer on stent implantation and elimination of long-term (>6 months) polymer exposure compared with durable polymer surface-coated stents, such as Taxus (Boston Scientific, Maple Grove, Minnesota), in theory might favorably influence both short- and long-term inflammatory and thrombogenic events. Drug dose, direction (luminal vs. abluminal), and kinetics of delivery are varied by drug-polymer mixing on a reservoir-by-reservoir basis. The precision of these variations in drug delivery has been shown to reach biologically meaningful proportions in several independent human trials, from which the 10 μg/30 day drug–PLGA reservoir load was selected based on the associated angiographic late lumen loss at 4 to 12 months (9–11). Such precision in a lower range of paclitaxel dosing in theory might provide similar efficacy but greater safety margin in settings such as provisional stent overlap compared with the higher dose delivered with the Taxus stent.

The COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study was designed to compare the 8-month clinical outcomes of patients with both single- and multivessel coronary stenoses undergoing elective percutaneous coronary intervention (PCI) with either the CoStar or the Taxus DES. In addition, the biological behavior of vessels treated with each of these stents was examined in smaller cohorts, in whom protocol-specified 9-month angiography was performed.

Methods

Study design and population. The COSTAR II study design has been previously described in detail (12). In summary, COSTAR II was a multicenter, prospective, single-blind, 3:2 (CoStar:Taxus) randomized study testing noninferiority of the CoStar versus the Taxus paclitaxel DES. In total, 1,700 patients were enrolled from 71 sites in the U.S., Germany, Belgium, and New Zealand. Anatomic eligibility required a de novo single target lesion of >50% but <99% stenosis in 1, 2, or 3 native epicardial coronary arteries, with a reference vessel diameter from 2.5 to 3.5 mm and a lesion length of <30 mm that could be covered with a single stent. Anatomic exclusion criteria included ostial lesions, left main coronary disease of >50% stenosis, bifurcation lesions with >2 mm side branch involvement, total occlusions, presence of a previously implanted DES proximal to target lesion site, or >50% stenosis elsewhere in the target vessel. Clinical exclusion criteria included myocardial infarction (MI) within 72 h, prior revascularization within 3

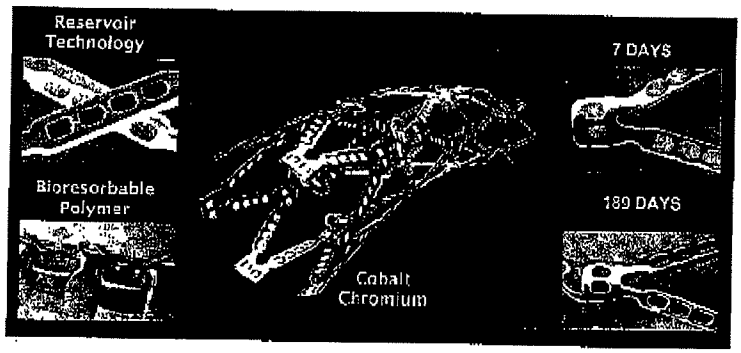

Figure 1 The CoStar Stent

The CoStar stent reservoir technology at 7 days and at 6 months.

JACC Vol. 51, No. 16, 2008
April 22, 2008:1543–52

months, intolerance of clopidogrel or aspirin, known bleeding diathesis, renal failure, left ventricular ejection fraction <25%, and contraindication to coronary artery bypass surgery. Approval by each participating institution's ethics committee and informed consent from all patients were required and obtained.

Pre-specified subgroup analyses included patients with multivessel disease, patients with diabetes, and patients requiring the provisional use of overlapping stents.

Protocol-mandated procedures. Repeat cardiac catheterization was planned 9 months after the index procedure in the first 250 patients enrolled with multivessel coronary artery disease and the first 100 patients with single-vessel disease. Of these 100 single-vessel patients, the first 70 also had planned protocol-specified intravascular ultrasound (IVUS) evaluation at the 9-month catheterization. In addition, all patients with (provisional) overlapping stents also underwent repeat catheterization and IVUS at 9 months. Serial blood sampling for pK analysis was performed in 45 patients, including 16 patients with multivessel stenting. A hemoglobin A1c level was obtained at baseline in all patients.

Device description. The CoStar stent is a 0.0035-inch thick cobalt chromium alloy metal platform with nondeformable strut segments that contain multiple laser-cut holes (12). Each hole is individually filled with a bioabsorbable PLGA polymer matrix combined with paclitaxel, creating discrete reservoirs of drug elution. Abluminal and/or endoluminal direction, total drug dose, and kinetics of drug delivery are controlled by programmed alterations in the ratio of bioabsorbable polymer to drug for each reservoir. The PLGA polymer resorption is complete in the porcine model by 180 days, thus leaving only the bare-metal platform in perpetuity. Based on serial comparative human studies of paclitaxel dose, direction, and kinetics of delivery (9–11), the CoStar stent selected for the COSTAR II study was the 10 μg/30 day elution drug-polymer formulation.

Randomization. Patients were randomly assigned 3:2 to CoStar or Taxus using an interactive voice randomization system. Randomization was stratified by single- or multivessel status. Patients were blinded to treatment assignment until after completion of 1 year of follow-up.

Stenting procedure. Antiplatelet therapy with a minimum of 325 mg aspirin and a loading dose of at least 300 mg clopidogrel, and intracoronary nitroglycerine for vessel sizing before stent implantation were required. Pre-dilatation of all lesions was also required. Planned use of a nonballoon device (rotational or directional atherectomy, laser, or any unapproved technology) was prohibited. Selection of U.S. Food and Drug Administration (FDA)-approved anticoagulant therapy and use of adjunctive glycoprotein IIb/IIIa inhibitors were at each operator's discretion. High-pressure post-dilatation was recommended but not required. Intravascular ultrasound other than the protocol-mandated use described in the preceding was at the discretion of the operator.

Dual antiplatelet therapy. Continuation of 325 mg aspirin and 75 mg clopidogrel daily for at least 6 months was required by protocol. For patients requiring warfarin sodium therapy, an aspirin dose of 81 mg daily was recommended. Decisions on interruption of dual antiplatelet therapy in case of bleeding or urgent surgery or on extension of clopidogrel therapy beyond 6 months were all managed clinically. Details of all such decisions were systematically captured and collected by the data coordinating center.

Clinical follow-up. Pre-specified clinical follow-up included at index hospital discharge, 30 days, 8 months, and 1 year. Patients with protocol-driven angiographic follow-up for any reason were required to have their 8-month clinical evaluation completed before their 9-month angiogram or IVUS.

Data management. All clinical data were double data entered into a Clintrials database at a central facility (Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina).

Clinical events committee. Events independently and blindly reviewed by the clinical event committee (CEC) (Duke Clinical Research Institute, Duke University Medical Center) included major adverse cardiac events (MACE), stent thrombosis, and total occlusion. In conjunction with FDA approval of COSTAR II as an investigational device exemption protocol, the definition of stent thrombosis was taken from the Taxus IV study (2), as detailed subsequently. The entire protocol was completed before the later publication of the consensus Academic Research Consortium definition (13) for stent thrombosis.

Core laboratories. ANGIOGRAPHY CORE LABORATORY. All angiograms were analyzed by an independent core laboratory (Quantitative Coronary Angiography [QCA] Core Laboratory, Cardiology Research Foundation, New York, New York). Angiograms were acquired using standardized instructions. The QCA was performed using the Cardiovascular Measurement System-Gradient Field Transform algorithm (Medis, Leiden, the Netherlands) (2). The minimum lumen diameter and the mean reference diameter, obtained from averaging 5-mm segments proximal and distal to the target lesion location, were used to calculate the diameter stenosis (diameter stenosis = [1 − minimum lumen diameter/reference diameter] × 100). Acute gain was the change in minimum lumen diameter from baseline to final post-stent implantation angiogram; late loss was the change in minimum lumen diameter from the final post-stent implantation angiogram to follow-up. Binary restenosis was defined as >50% diameter stenosis in the index vessel. All quantitative measurements were performed: 1) within the stented segment (in-stent); 2) in-segment, spanning the stented segment plus the 5 mm proximal and distal peristent areas; and 3) in the 5 mm proximal and distal peristent areas immediately adjacent to the stent.

IVUS CORE LABORATORY. Blinded IVUS analysis of 70 subjects post-procedure and at 9 months was done by an

independent core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University Medical Center, Stanford, California). All images were reviewed by 2 independent observers, and adjudication of opinion was based on consensus of these observers. Volumetric measurements were performed using planimetry software (echoPlaque, Indec Systems, Santa Clara, California) as previously described and included persistent plaque volume, neointimal volume, percent neointimal obstruction, neointimal coverage, and neointimal thickness (14). Incomplete stent apposition was defined as 1 or more struts clearly separated from the vessel wall with evidence of blood speckles behind the strut.

ELECTROCARDIOGRAPHY CORE LABORATORY. Standard 12-lead electrocardiograms (ECGs) were collected before PCI, before hospital discharge, and at 8-month follow-up and forwarded to an independent core laboratory (ECG Core Laboratory, Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina). The ECGs were analyzed for new pathological Q waves by an experienced cardiologist blinded to treatment assignment.

End points. The primary end point of the COSTAR II study was 8-month MACE, defined as a hierarchical composite of cardiac or unknown cause of death, Q-wave and non–Q-wave MI, and clinically driven target vessel revascularization (TVR). This time point was selected specifically to allow completion of all clinical outcomes reporting before any protocol (9 month) catheterizations. Q-wave MI was defined as: 1) clinical presentation with signs or symptoms of MI with new pathological Q waves as determined by the ECG core lab or independent review of the CEC in the absence of timely cardiac enzyme data; or 2) new pathological Q waves as determined by the ECG core lab or independent review of the CEC and elevation of cardiac enzymes. Non–Q-wave MI was defined as elevated creatine kinase (CK) ≥2 times the upper limit of normal with elevated CK-MB in the absence of any new pathological Q waves. "Clinically driven TVR" was defined as a revascularization of the target vessel with: 1) anginal symptoms and/or functional ischemia with a ≥50% stenosis by core lab QCA; or 2) revascularization of ≥70% stenosis by the core lab QCA. All deaths and MI events were counted as MACE events unless the CEC unequivocally attributed them to either a nontarget vessel or noncardiac cause. The primary angiographic end point was per-vessel 9-month angiographic in-segment late lumen loss.

Secondary end points included the individual MACE components, 30-day and 12-month MACE, clinically driven target lesion revascularization, and target vessel failure, as were reported in the pivotal Taxus IV study (2). Secondary technical end points included device success (final stenosis of <50% using the assigned device only), lesion success (final stenosis of <50% using any device), and procedure success (final stenosis of <50% with no procedure-related MACE). Stent thrombosis was categorized as acute (before leaving the catheterization laboratory), subacute (after the index procedure and within 30 days), and late (after 30 days). Acute stent thrombosis was defined as abrupt vessel closure of the treatment site resulting in clinical manifestations of ischemia and angiographic evidence of occlusion or flow-limiting thrombosis in a treated vessel, in which the investigational device was successfully implanted, that occurred after the procedure but before the patient left the catheterization laboratory. Subacute stent thrombosis was defined as abrupt vessel closure of the treatment site producing clinical manifestations of ischemia and occlusion occurring after the patient left the catheterization laboratory but within 30 days of the interventional procedure. Late stent thrombosis was defined as MI attributable to the target vessel, with angiographic documentation of thrombus or total occlusion at the target lesion >30 days following successful implantation of the device.

Statistical analysis. The primary end point (8-month MACE) analysis (12) was a noninferiority analysis using either the relative risk or the absolute difference in rates between the CoStar stent rates and the Taxus stent rates, depending on the actual MACE rate observed in the Taxus (control) arm. If the actual MACE rate in the Taxus arm was ≥10%, then the observed relative risk was to be compared with a relative delta of 1.5, calculated using statistical software (Proc Genmod, SAS, Cary, North Carolina) using a log link function. If the actual 8-month MACE rate in the Taxus arm was <10%, then an absolute delta of 5% was to be used, calculated using software (StatXact, Cytel, Cambridge, Massachusetts) to provide asymptotic and exact confidence intervals for a difference in proportions.

In conjunction with discussions with the FDA for this pivotal study, a series of consistency analyses were prespecified to provide "reasonable assurance" of safety and effectiveness of the CoStar stent. As has previously been detailed (12), these consistency analyses were additive and based on confidence intervals specifically calculated with regard to the denominator of each subgroup (e.g., angiographic cohort, single-vessel cohort), not as serial comparisons per se. Thus, if 8-month MACE rates from the primary end point analysis met the boundaries specified, then 2 consistency analyses were to be computed to confirm noninferiority using the pre-specified confidence intervals. The 9-month angiographic in-segment late loss was to be analyzed on a per-vessel basis using the protocol-specified angiographic cohort. An absolute difference in 9-month late loss between the Taxus group and the CoStar group was to be estimated. A 95% confidence interval was to be constructed around this estimate using a statistical analysis procedure (Proc Mixed, SAS) with the repeated statement. If this confidence interval fell completely below 0.32 mm, then noninferiority of the CoStar stent relative to the Taxus stent would be confirmed by the late loss observations. If the confidence interval overlapped or fell completely above 0.32 mm then noninferiority would not be confirmed.

JACC Vol. 51, No. 16, 2008
April 22, 2008:1543–52

Finally, if the preceding 2 conditions were met, then a third confirmatory test for angiographic late loss was to be performed using only the single-vessel stratum of angiographic cohort patients, using the same analytic methods as the preceding but with the relative delta set at 1.65 and the absolute delta set at 7% to accommodate the smaller denominator of patients.

If all 3 conditions described were met (per-patient 8-month MACE, per-vessel late lumen loss in entire angiographic cohort, and per-vessel late lumen loss in single-vessel angiographic cohort), then the CoStar device was to be declared to be noninferior to the Taxus device.

In the absence of any previous trial comparing the CoStar stent with an FDA-approved bare-metal stent, a final step was included in the primary statistical analysis plan: an imputed placebo calculation (12). For this analysis, the primary end point was estimated for a bare-metal stent against the experimental CoStar DES in the single-vessel disease population, because bare-metal stent data versus Taxus DES was only available for single-vessel disease patients at the time COSTAR II was designed. This analysis used the formulas and logic previously detailed by Hasselblad and Kong (15). The hypothesis was tested in the relative risk space (CoStar vs. placebo) regardless of the COSTAR II Taxus arm outcome rate. The estimate and variance used for the effect of standard treatment relative to placebo was taken from previously published pooled data for the Taxus IV (2), V (16), and VI (17) studies. If the confidence interval for the estimate of experimental treatment relative to placebo was completely to the left of 1.0, it would be taken to indicate that the CoStar stent was better than a bare-metal stent would have been.

Continuous data are presented as means, and categorical variables are presented as percentages, unless otherwise noted. Selected baseline characteristics and clinical and angiographic outcomes are compared between treatment groups by the chi-square test in case of discrete variables and *t* test in case of continuous variables. A p value of <0.05 was considered to be statistically significant. No statistical adjustment was made for multiple comparisons. All analyses were done using SAS version 8.0 or higher statistical software.

Results

Patient and lesion characteristics. Of the 1,700 patients randomly assigned, 1,675 (98.5%) were evaluable and constituted the primary study population (Fig. 2). The 25 derandomized patients were excluded because: 1) angiographic inclusion criteria could not be confirmed at the time of the index PCI procedure; or 2) the study-assigned stent was never removed from the packaging or advanced beyond the guide catheter. Of the 1,675 patients, 989 were randomly assigned to receive treatment with the CoStar DES and 686 with the Taxus DES in the asymmetric 3:2 design. Clinical descriptors and target lesion characteristics were evenly distributed across treatment groups (Table 1). Of the 1,675 patients, 1,330 (79%) had single-vessel intervention and 345 (21%) had multivessel intervention. In total, 2,058 target lesions were treated, 1,212 (59%) with CoStar and 846 (41%) with Taxus. Procedural glycoprotein IIb/IIIa inhibitors were used in 20.5% of all patients (20.2% for CoStar, 20.9% for Taxus).

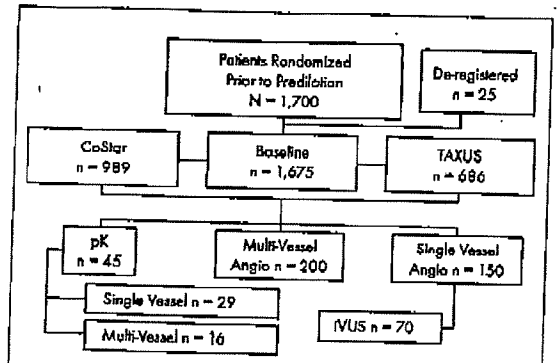

Figure 2 Patient Flow Diagram

Of the 1,700 patients randomly assigned, 1,675 were evaluable and constituted the primary study population. IVUS = intravascular ultrasound.

Procedural characteristics. On a per-vessel analysis, device success was analyzable in 2,049 (99.6%) of 2,058 lesions. Of these 2,049, device success was achieved in 1,173 (97.3%) of 1,205 lesions with CoStar (single-vessel 794 of 813 [97.6%], multivessel 379 of 392 [96.7%]) and in 825 (97.7%) of 844 lesions with Taxus (single-vessel 539 of 552 [97.6%], multivessel 286 of 292 [97.9%]), and lesion success was achieved in 100% and 99.9%, respectively. On a per-patient analysis, procedural success was achieved in 957 (97.4%) of 983 patients with CoStar (single-vessel 770 of 786 [97.9%], multivessel 187 of 197 [94.9%]), and in 672 (98.2%) of 684 patients with Taxus (single-vessel 532 of 539 [98.7%], multivessel 140 of 145 [96.6%]). None of these differences were significant.

Clinical outcomes. Periprocedural/index hospitalization hierarchical MACE was 2.6% with CoStar (0% death, 2.4% MI, 0.2% clinically driven TVR) and 1.6% with Taxus (0% death, 1.6% MI, 0% clinically driven TVR); p = 0.160. The rate of MACE at 30 days was 3.4% with CoStar (0% death, 2.8% MI, 1.0% clinically driven TVR) and 1.9% with Taxus (0% death, 1.6% MI, 0.2% clinically driven TVR); p = 0.063. In patients with single-vessel disease, periprocedural/index hospitalization hierarchical MACE was 2.0% with CoStar (0% death, 1.9% MI, 0.1% clinically driven TVR) and 1.3% with Taxus (0% death, 1.3% MI, 0% clinically driven TVR); p = 0.3131. The rate of MACE at 30 days was 3.1% with CoStar (0% death, 2.4% MI, 1.0% clinically driven TVR) and 1.5% with Taxus (0% death, 1.3% MI, 0.2% clinically driven TVR); p = 0.0711. In patients with multivessel disease, periprocedural/index hospitalization hi-

Table 1 Clinical Descriptors and Lesion Characteristics

	Total (n = 1,675)	CoStar* (n = 989)	Taxus* (n = 686)	CoStar Single-Vessel (n = 789)	Taxus SingleVessel (n = 541)	Costar Multivessel (n = 200)	Taxus Multivessel (n = 145)
Patient characteristics, % (unless otherwise specified)							
Male	72.8	73.1	71.1	72.1	69.3	77.0	77.9
Age, mean ± SD (yrs)	63.6 ± 10.7	63.5 ± 10.8	63.7 ± 10.6	63.4 ± 10.9	63.4 ± 10.6	64.0 ± 10.8	64.8 ± 10.2
Prior MI	28.9	26.3	27.7	26.5	28.3	25.5	25.5
Prior PCI	33.1	33.5	32.7	35.0	34.4	27.5	26.2
Prior CABG	6.2	6.4	6.0	7.0	6.7	4.0	3.4
Diabetes mellitus	28.0	27.4	28.9	27.0	29.0	29.0	28.3
IDDM*	25.0	27.7	21.3	26.3	21.2	32.9	22.0
Hyperlipidemia	79.8	80.5	78.9	81.6	80.2	76.0	73.8
Hypertension	77.8	77.9	77.7	77.3	78.6	80.0	74.5
Unstable angina	30.5	29.4	32.1	28.9	31.6	31.5	33.8
Current smoker	20.8	20.1	21.9	20.7	22.2	18.0	20.7
LVEF, mean ± SD (%)	58.2 ± 11.7	58.0 ± 11.6	58.5 ± 11.8	57.9 ± 11.5	58.7 ± 11.6	58.1 ± 12.0	57.8 ± 12.2
Multivessel treatment	20.6	20.2	21.1	0	0	100.0	100.0
Lesion characteristics, % (unless otherwise specified)							
RVD, mean ± SD (mm)	2.76 ± 0.47	2.77 ± 0.47	2.75 ± 0.48	2.78 ± 0.46	2.78 ± 0.49	2.75 ± 0.48	2.69 ± 0.46
MLD, mean ± SD (mm)	0.87 ± 0.41	0.86 ± 0.40	0.89 ± 0.41	0.86 ± 0.40	0.88 ± 0.42	0.87 ± 0.41	0.90 ± 0.41
B2/C lesion class	60.0	58.9	61.5	61.0	64.6	54.5	55.6
Moderate/heavy calcification	25.6	25.8	25.3	25.0	25.3	27.6	25.4
LAD	40.1	39.9	40.3	41.9	41.3	35.9	38.2
Circumflex	27.9	27.9	30.6	26.3	27.8	31.1	35.8
RCA	31.0	32.2	29.2	31.8	30.9	33.1	25.9
Lesion length, mean ± SD (mm)	15.2 ± 6.5	15.4 ± 6.6	15.1 ± 6.5	15.01 ± 6.28	14.83 ± 6.29	16.06 ± 6.82	15.53 ± 6.77
Average stent diameter per vessel, mean ± SD (mm)	2.98 ± 0.55	2.95 ± 0.57	2.96 ± 0.50	2.96 ± 0.56	2.96 ± 0.58	2.68 ± 0.44	2.64 ± 0.41
Total stented length, mean ± SD (mm)	20.5 ± 7.6	20.7 ± 7.8	20.1 ± 7.4	20.56 ± 8.02	19.82 ± 7.46	21.06 ± 7.33	20.70 ± 7.14
Overlap stenting, n	168	108	60	73	36	35	24

*For all comparisons, p = nonsignificant.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; IDDM = insulin-dependent diabetes mellitus; LAD = left anterior descending; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; RCA = right coronary artery; RVD = reference vessel diameter.

erarchical MACE was 5.0% with CoStar (0% death, 4.5% MI, 1.0% clinically driven TVR) and 2.8% with Taxus (0% death, 2.8% MI, 0% clinically driven TVR); p = 0.2977. The rate of MACE at 30 days was 5.0% with CoStar (0% death, 4.5% MI, 1.0% clinically driven TVR) and 3.5% with Taxus (0% death, 2.8% MI, 0.7% clinically driven TVR); p = 0.4794. Table 2 shows MACE at 8 months, the primary study end point, and each of its components. The rate of MACE was significantly lower with Taxus than with CoStar, a difference due predominantly to the difference in clinically driven TVR rates. At 8 months, both MI and mortality rates were not significantly different. The MACE to 8 months is shown discretely for both the single- and the multivessel subgroups (Table 2). The absolute difference between observed event rates between Taxus and Costar groups with multivessel PCI is numerically larger than in the single-vessel cohort, but with the smaller number of patients does not reach statistical significance.

The temporal distribution of hierarchical MACE and its component events are shown in Kaplan-Meier curves to completed 9-month follow-up in Figure 3. The impact of 513 protocol catheterizations (100 single-vessel, 250 multivessel, 168 patients with overlapped stents [60 with Taxus, 108 with CoStar]) on TVR events from 8- to 9-month follow-up can be discretely appreciated. In this 1-month interval, additional MACE events produced an absolute increase in event rates of 2.4% in Taxus patients and 3.7% in CoStar patients, numerically increasing the difference between the 2 cohorts. The Kaplan-Meier curves of death and Q-wave MI show no significant differences at any time, whereas the clinically driven TVR curves begin to separate between 30 and 90 days after index PCI.

Odds ratios of 8-month hierarchical MACE are shown for all pre-specified subgroups in Figure 4. Differences do not reach statistical significance in many of the subgroups owing to small denominators; however, numerical differences and trends consistently favor the Taxus treatment group.

Per-vessel angiographic outcomes. Angiographic results at 9 months from 456 lesions in 286 patients (262 lesions CoStar, 194 lesions Taxus) are shown in Table 2. Per-vessel in-stent and in-segment late loss, diameter stenosis, and

JACC Vol. 51, No. 16, 2008
April 22, 2008:1543–52

Table 2 Clinical and Angiographic End Points

Parameter	CoStar (n = 989)	Taxus (n = 686)	p Value
8-month clinical end points (%)			
All MACE	11.0	6.9	0.005
Single-vessel MACE	9.9	6.1	0.015
Multivessel MACE	15.4	9.7	0.125
Death	0.5	0.7	0.541
MI	3.4	2.4	0.242
Clinically-driven TVR	8.1	4.3	0.002
9-month angiographic end points			
Late loss (mm)			
In-stent	0.64	0.26	<0.0001
In-segment	0.49	0.18	<0.0001
Diameter stenosis (%)			
In-stent	25.32	12.83	<0.0001
In-segment	31.89	23.95	<0.0001
BAR (%)			
In-stent	17.9	4.1	<0.0001
In-segment	18.7	6.7	0.0002

BAR = binary angiographic restenosis; MACE = major adverse cardiac events; MI = myocardial infarction; TVR = target vessel revascularization.

binary restenosis were all significantly better in the Taxus group compared with the CoStar group.

Stent thrombosis. Both overall and time-related incidence of protocol-defined stent thrombosis are shown in Table 3. The 1 patient with acute thrombosis had coronary perforation during the index procedure, which was treated with a stent graft (Jomed International, Helsingborg, Sweden). Recurrent instability while still in hospital led to recatheterization, which showed thrombus on the stent graft that was treated medically without further complications. Of the 4 CoStar patients with subacute stent thromboses, 1 (thrombosis on day 3) was found to be dual antiplatelet therapy resistant, 2 (thromboses on days 6 and 9) were clopidogrel noncompliant, and antiplatelet therapy compliance was indeterminate in 1 patient. Both patients who suffered late thrombosis did so within days of stopping their clopidogrel (day 177 for CoStar, day 232 for Taxus). All stent thromboses were associated with MI, none with death.

Imputed placebo. The relative risk of 8-month MACE outcomes with the CoStar stent versus the imputed placebo of the Express bare-metal stent is shown in Figure 5. Confidence intervals of CoStar 8-month MACE cross the unity line, suggesting that use of the CoStar stent produced no significant difference from the imputed outcomes with a bare-metal stent placebo.

Discussion

In this prospective, randomized, multicenter study of 2 paclitaxel-eluting stent platforms, per-patient primary clinical outcomes at 8 months and per-vessel angiographic end points at 9 months demonstrated significant differences between the Taxus DES versus the CoStar DES, with the result that it cannot be concluded that CoStar DES is noninferior to Taxus DES. Divergence between the clinical event curves begins around 3 months, is numerically exaggerated by oculostenotic events at 9 months, and is predominantly driven by TVR (MI and death rates remain essentially the same between devices over that time). This

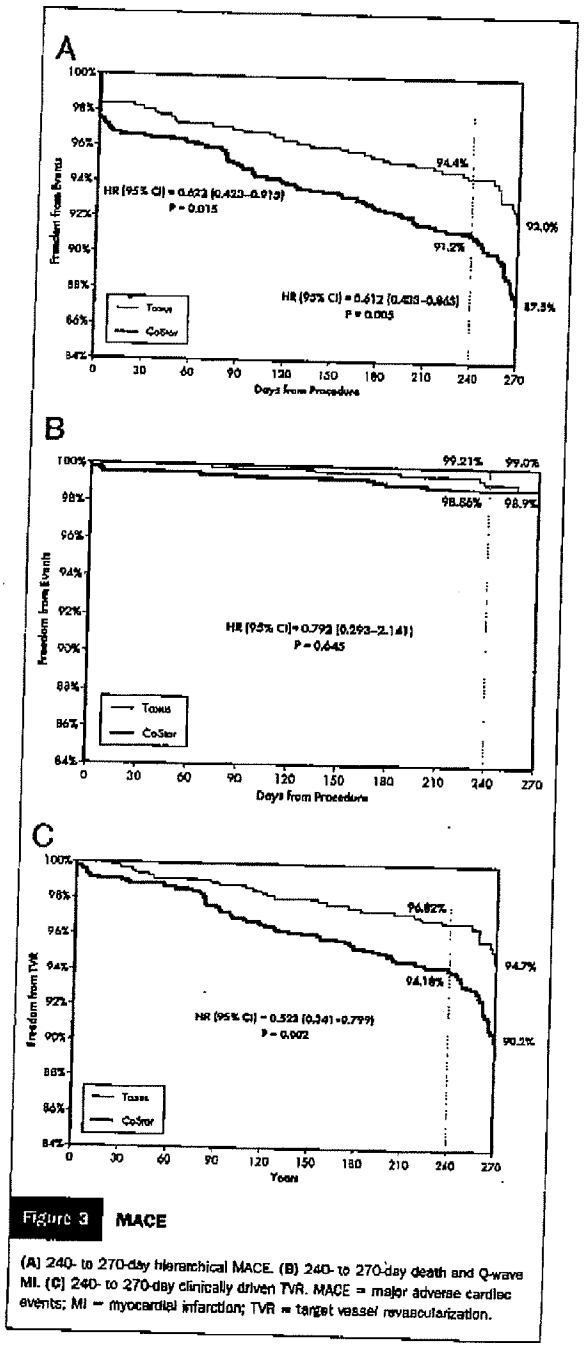

Figure 3 MACE

(A) 240- to 270-day hierarchical MACE. (B) 240- to 270-day death and Q-wave MI. (C) 240- to 270-day clinically driven TVR. MACE = major adverse cardiac events; MI = myocardial infarction; TVR = target vessel revascularization.

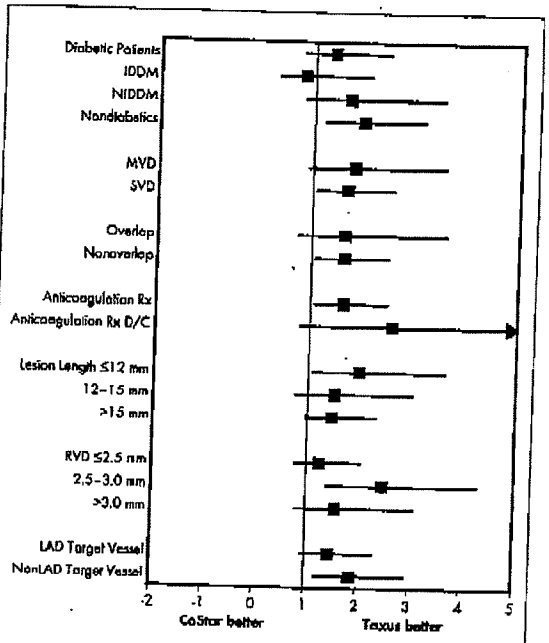

Figure 4 MACE in Subgroups

Eight-month hierarchical MACE in pre-specified subgroups. D/C = discontinued; IDDM = insulin-dependent diabetes mellitus; LAD = left anterior descending artery; MACE = major adverse cardiac events; MVD = multivessel disease; NIDDM = noninsulin-dependent diabetes mellitus; RVD = reference vessel diameter; Rx = prescription; SVD = single-vessel disease.

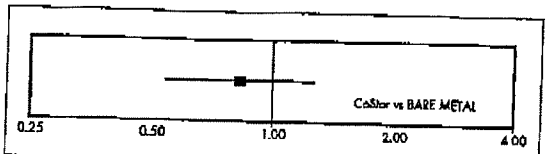

Figure 5 Relative Risk

Relative risk of CoStar versus imputed placebo 8-month major adverse cardiac events.

strongly suggests the mechanistic hypothesis that fibrointimal hyperplasia resulting in in-stent restenosis is greater with the CoStar stent than with the Taxus stent. The per-vessel angiographic findings at 9 months also support this mechanistic explanation. Finally, the imputed placebo calculation implies that the CoStar stent is not superior to bare-metal stents, which have been shown to have significantly higher in-stent restenosis rates than the Taxus stent in randomized controlled clinical trials (2).

Secondary analyses of multiple subgroups, including the 3 pre-specified groups (single- vs. multivessel disease, diabetes, and patients with overlapping stents), were highly consistent with the primary study results. No significant increase in the risk of death, MI, or stent thrombosis was appreciated in any subgroup.

Table 3 Protocol-Defined Stent Thrombosis

	CoStar	Taxus	p Value
Acute (<24 h)	0.1% (1)	0.0% (0)	NS
Subacute (1–30 days)	0.4% (4)	0.0% (0)	NS
Late (1–9 months)	0.1% (1)	0.1% (1)	NS
Total stent thrombosis	0.6% (6)	0.1% (1)	0.25

NS = not significant.

The CoStar DES incorporates a number of unique features with theoretic appeal compared with the Taxus stent (12). Whereas the Taxus DES was developed by applying a surface coating of durable polymer to the bare-metal Express platform, the CoStar stent was designed specifically for drug delivery via individual wells filled with drug and polymer (12). Initial studies that evaluated the optimal drug load and kinetics of paclitaxel delivery using the CoStar platform were encouraging. The PISCES (Paclitaxel In-Stent Controlled Elution Study) study examined 6 different drug, direction, and duration of elution configurations, and the COSTAR I study independently evaluated dose optimization using 3 configurations (9,10). Both early (4 months) and late (12 months) angiographic surrogate measures suggested that the abluminal unidirectional 10 μg/30 day and 30 μg/30 day stent loads effectively preserved in-segment and in-stent late lumen loss (9,10). These 2 formulations were then tested head to head in the EUROSTAR (European Cobalt Stent With Antiproliferative for Restenosis) trial, where the 10 μg/30 day platform was found to result in lower levels of late lumen loss in human subjects (11). Based on this series of human dose-finding investigations, the 10 μg/30 day load was selected for the pivotal COSTAR II study.

Despite theoretic design novelty and the consistent legacy of previous small trial performance with 4- to 12-month in-segment late loss values of <0.3 mm with the 10 μg/30 day formulation, the results of the pivotal COSTAR II trial serve as a reminder of the importance of adequately sized and well designed trials conducted in contemporary patient cohorts (9–11). Notably, in COSTAR II, the CoStar stent performed worse than in preceding trials and the Taxus stent performed better than in its pivotal study (Taxus IV), despite the more complex patient cohort in COSTAR II. Potential explanations for under- or over-performance are speculative, but include small previous study size with wide confidence intervals, differences in device manufacturing process (CoStar), and operator familiarity and learning curve (Taxus).

The COSTAR II study represents the actual implementation of a different set of key principles outlined in the early anticipation of the challenges of active-control studies of DES. Instead of emphasizing the use of surrogate angiographic measures in simple patients, COSTAR II enrolled a more complex ("enriched") patient population in whom a

JACC Vol. 51, No. 16, 2008
April 22, 2008:1543–52

higher density of clinical events would be expected (18). This strategy supports a logistically feasible clinical trial that also provides pre-market data with greater relevance to real-world post-market use (18). Furthermore, by enriching the angiographic cohort with multivessel patients, the ethical and logistic issues associated with mandated repeat catheterization were minimized, which is a key feature when patients have the alternative of receiving an approved DES without participation in the research study. Indeed, the COSTAR II trial has the smallest percentage of patients subjected to protocol recatheterization of any published pivotal DES study. In addition, by completing the clinical outcome evaluation 30 days before protocol-specified catheterization, the impact of oculostenotic events could be discretely appreciated. A number of these study design features are among recommendations for future DES pivotal trials (19).

The statistical analysis of an enriched population in an active control noninferiority study design is unique as well. At the time COSTAR II was being planned, multivessel stenting with the Taxus DES was widely practiced in post-market use, but it was not an approved indication for the device and had not been reported in a randomized clinical trial. Thus, the COSTAR II control group also represented an "exploratory" population (e.g., one without a clearly definable predicate) (12). The statistical analysis plan developed a noninferiority delta as a relative risk to the actual observed event rate in the control group over a range of possibilities and supported the relative risk delta with an imputed placebo calculation to ensure that the confidence intervals at the high end of the delta would not reach the lowest event rates expected from bare-metal stents.

Study limitations. There are a number of limitations worth noting from this report. Initially, the hope was to enroll 50% multivessel patients; however, this proved to be unfeasible. Nonetheless, the 20% enrolled represent the first advance to more "enriched" populations in pivotal DES studies. In addition to the multivessel group, there are many other key subgroups that remain relatively underpowered for noninferiority comparisons, despite the fact that COSTAR II is larger than any previously reported pivotal DES trial. The IVUS findings in the very small number of single-vessel and overlap cases acquired are not included in the present report, and they might offer further mechanistic insights into the behavior of both CoStar and Taxus stents in these populations. However, the clinical and angiographic findings are all so consistent that it is unlikely that IVUS would affect any of the conclusions from this primary study report.

Although clearly not noninferior, safety issues between Taxus and the CoStar DES platforms remain of interest. By 9 months of follow-up no differences in safety parameters were observed between devices. The COSTAR II study was designed before widespread awareness of infrequent but catastrophic events, such as late stent thrombosis, and is not powered for such comparisons, particularly within such a short follow-up period. Further insights may be gained when longer-term follow-up is completed and integrated with the detail of actual duration of dual antiplatelet therapy, therapy interruption, and so on. Finally, although the definition of stent thrombosis used in COSTAR II was developed primarily for comparability with Taxus IV, the subsequent emergence of the Academic Research Consortium stent thrombosis definitions may make readjudication of these events useful to support comparability with other DES platform experiences (13).

Conclusions

The COSTAR II study demonstrates that it cannot be concluded that the CoStar DES is noninferior in clinical and angiographic performance compared with the Taxus DES. The relative benefit attributable to the Taxus stent is predominantly due to lower rates of clinically driven TVR, with no differences observed in the incidences of death, MI, or stent thrombosis by the end of 9 months' follow-up.

Author Disclosures

Duke University received significant grant revenue from Conor MedSystems as the enrolling site; none of this revenue went to Dr. Krucoff or his salary. Duke Clinical Research Institute received grant money for clinical trial operations. Duke Clinical Research Institute also receives significant grant support from competitive companies including Terumo, Cordis Johnson & Johnson, Abbott, Medtronic, and Boston Scientific. Dr. Krucoff has received consulting fees and honoraria (modest) from Conor MedSystems, Cordis Johnson & Johnson, Abbott, Medtronic, OrbusNeich, Affinergy, Biosensors, and Terumo. Dr. Kereiakes has received research grants (modest) from Conor MedSystems, Pfizer, Cordis Johnson & Johnson, Boston Scientific, Medtronic, and Daiichi-Sankyo; received consulting fees (modest) from Conor MedSystems, Cordis Johnson & Johnson, Core Valve, Eli Lilly & Co., Boston Scientific, and Abbott Bioadsorbable Vascular Solutions; and served on the Speakers' Bureau of Eli Lilly & Co. Dr. Peterson has received a significant research grant from Conor MedSystems. Dr. Mehran has received modest research grants from Tyco Mallinkradt, Geurbet, and Cordis Johnson & Johnson and served on the Speakers' Bureau (modest) of The Medicines Company, Cordis Johnson & Johnson, and Boston Scientific. Dr. Fitzgerald received significant consulting fees from Conor MedSystems and Cordis Johnson & Johnson and honoraria from Cordis Johnson & Johnson. Dr. Turco has served as a consultant and on the Speakers' Bureau of Boston Scientific, Cordis, Medtronic, and Abbott Vascular; he has received research grants from Boston Scientific, Cordis, Medtronic, Abbott Vascular, Sanofi-Aventis, Lumen Biomedical, and EV3. Dr. Simonton is an employee of Abbott Vascular. Dr. Dubois served on the advisory board of Boston Scientific and received a research grant from Conor MedSystems. Dr. Batchelor received consulting fees from Conor MedSystems

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APPENDIX

For trial structure and participating sites, please see the online version of this article.

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Drug-eluting stents for the treatment of coronary artery disease Part 3: New results from clinical trials

By MICHAEL J. B. KUTRYK, MD, PhD, FRCPC

Since the first reports of the success of drug-eluting stents for prevention of in-stent restenosis by Sousa et al and Rensing et al in 2001,[1,2] the implantation of drug-eluting stents has become the percutaneous treatment of choice for many coronary lesion subsets. The June/July and August/September 2002 issues of *Cardiology Rounds* presented Part 1 and Part 2 of a review of drug-eluting stents for the treatment of coronary artery disease. In Part 1 of this series, the discussion focused on the rationale behind the development of a stent with a bioactive coating and the early trials using paclitaxel-eluting coatings. Part 2 focused on rapamycin and other cytostatic and cytotoxic drugs that were undergoing clinical evaluation at that time. In the last year, there has been important new information provided by many multicentre clinical studies. Parts 3 and 4 of this series provide an update of the results of trials that were ongoing when Parts 1 and 2 were published last year and summarizes the new clinical data.

Clinical trials with sirolimus-eluting stents

Trials examining sirolimus, (rapamycin, Rapamune®) coated devices were among the first to provide concrete evidence that drug-eluting stents had the potential to prevent restenosis. Sirolimus is a natural macrocyclic lactone produced by *Streptomyces hygroscpicus* with potent antiproliferative, anti-inflammatory, and immunosuppressive effects. Because of its lipophilicity, sirolimus easily passes through cell membranes and binds to an intracellular binding protein (immunophilin) known as FK binding protein-12 (FKBP-12). The sirolimus/FKBP-12 complex inhibits the activation of the mammalian target of rapamycin (mTOR), a key regulatory serine-threonine kinase. The inhibition of mTOR inhibits the translation of a family of mRNAs that code for proteins essential for cell cycle progression and induces the cyclin-dependent kinase inhibitor p27, ultimately causing cell cycle arrest.

First studies with the sirolimus-eluting stent

Results of the first human implantations of sirolimus-eluting (Bx Velocity) stents, the first-in-man (FIM) clinical studies were reported by Sousa et al[1] and Rensing et al.[2] A total of 45 patients with symptomatic coronary artery disease and a single *de novo* lesion were included, 30 patients in São Paolo and 15 in Rotterdam. The study was designed to test the feasibility of implanting sirolimus-eluting Bx Velocity stents. Thirty patients received a slow-release device, while 15 were treated with fast-release stents. Planned endpoints included 1-month, 6-month, and 5-year assessment of major adverse cardiac events (MACE). Four month, 1-year, 2-year, and 4-year quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) analysis were also planned. The follow-up of 30 patients (15 slow-release and 15 fast-release)[1] and the 4-month follow-up of 30 patients[3] was reported by Sousa et al. There was minimal intimal hyperplasia in both groups as determined by:

- IVUS (0.3 ± 0.6 slow-release and 0.3 ± 0.8 fast-release, volume % neointimal hyperplasia; P=NS), or
- QCA, (0.09 ± 0.3 slow-release and -0.1 ± 0.3 fast-release mm in-stent late loss (post-procedural minimal luminal diameter [MLD] minus 4-month follow-up MLD).[1,3]

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Rensing et al reported that there were no adverse cardiac events and no in-stent or edge restenosis (>50% diameter stenosis) observed at the 6-month angiographic follow-up of 13 of their 15-patient slow-release cohort.[2] These favourable results persisted to 12-month follow-up in the patients treated by Sousa as assessed by IVUS (2.3 ± 5.5% slow-release and 2.2 ± 3.4% fast-release, volume % neointimal hyperplasia; P=NS).[3] In-stent neointimal hyperplasia volume, as detected by IVUS, remained minimal after 2 years (fast-release = 6.3 ± 5.5%, slow release = 7.5 ± 7.3%; P=NS).[4] Two-year angiographic follow-up showed that only 1 patient (fast-release group) had a 52% diameter stenosis within the lesion segment that required repeat revascularization. The target-vessel revascularization rate for the entire cohort was 10% (3/30) at 2 years.

RAVEL

The remarkably good results from the Phase I clinical trial prompted the initiation of the Phase II trial, RAVEL (Randomized Study with the Sirolimus-eluting Bx Velocity Balloon Expandable Stent).[5] The trial enrolled 238 patients at 19 centres across Europe and Latin America. Patients were randomized to receive either a bare Bx Velocity stent, or a sirolimus-eluting Bx Velocity (Cypher™) stent coated with a 5 μm thick coating of sirolimus-polymer and received 2 months of ticlopidine or clopidogrel post-procedure. At 6-month follow-up, late loss in luminal diameter (primary endpoint) in the cohort treated with the sirolimus-eluting stent was 0.01 compared with 0.80 in the control group (P<0.0001). Binary restenosis rates (>50% diameter stenosis) among the 120 patients who received the drug-eluting device were reported as 0% compared with 26.2% in the group that received the uncoated stent. MACE rates were 3.3% in the treated group and 27.1% in the control group. Subacute stent thrombosis did not occur in either group. At 1-year, no repeat percutaneous transluminal coronary angioplasty (PTCA) of the target lesions were required for the sirolimus-eluting stent (SES) group (n=120), as compared with 13.6% of controls (16 of 118 patients). One bypass procedure was required in the SES group. After up to 2 years, there were no cardiac deaths. A second patient in the SES group required bypass surgery and 1 patient needed repeat PTCA (0.8%). Event-free (death, myocardial infarction [MI], coronary artery bypass graft [CABG], re-PTCA) survival was 90.0% for patients who received the sirolimus stents and was significantly higher than for controls (80.5%). Target lesion revascularization for sirolimus patients was extremely low at 2.5%. Stent thrombosis remained at 0%. Safety profiles were comparable in the two RAVEL arms.

SIRIUS

The U.S. randomized SIRIUS (Sirolimus US Eluting Stent in De Novo Coronary Lesions) trial – comparing the Cypher device to an uncoated Bx VELOCITY stent – is complete.[6] The SIRIUS trial was a randomized control trial at 53 investigational centres across the US, in 1058 subjects with single *de novo* coronary artery lesions. It was designed to examine the safety and efficacy of sirolimus-coated devices (slow-release, 140 μg sirolimus/cm^2) versus placebo. Subjects will be followed for 5 years. At the 8-month angiographic follow-up, sirolimus-treated patients had significantly lower rates of in-stent restenosis (3.2% vs 35.4%, P<0.001). At the 9-month clinical follow-up, the primary endpoint of target vessel failure (cardiac death, MI, target vessel revascularization) was significantly reduced by 59% in sirolimus-treated patients (8.5% vs 21.0%, P<0.001).

E-SIRIUS and C-SIRIUS

The E-SIRIUS (Europe and Latin America) and C-SIRIUS (Canada) clinical trials have recently been completed. These multi-centre, randomized, double-blind clinical trials randomized patients with single *de novo* coronary lesions. The primary endpoint of both trials was the maintenance of in-stent luminal diameter at 8-month follow-up. The E-SIRIUS trial involved 352 patients at 35 centres and was the first drug-eluting stent trial to allow the operators to employ a direct stenting technique (no pre-dilatation of the vessel before stenting).[7,8] Event-free survival in the sirolimus-treated patients was 95.9%, which was significantly better than 78.3% in the bare stent treated group (P<0.001). Binary restenosis rates were 4.0% in the sirolimus group compared with 42.3% in the control arm (P<0.001). There was no difference in outcome between a direct stenting technique and the more traditional technique involving pre-dilatation. The C-SIRIUS trial involved 100 patients at 8 sites. In-stent late loss at 8 months was 0.09 in the sirolimus-treated group and 1.01 in the bare stent group (P<0.0001). Event-free survival was 96.0% in the sirolimus-treated group and 81.7% in the bare stent group (P<0.05). The binary restenosis rate in the sirolimus group was 0% compared with 41.9% in controls (P<0.001).

The benefit of sirolimus-eluting stents in patients for the treatment of recurrent in-stent restenosis has also been demonstrated. Degertekin et al reported the results of the implantation of one or more Bx Velocity sirolimus-eluting stents in 16 patients with in-stent restenosis in a native coronary artery and objective evidence of ischemia.[9] Quantitative angiographic and IVUS follow-up was performed at 4 months, and clinical follow-up at 9 months. Four patients had recurrent restenosis following brachytherapy and 3 patients had totally occluded vessels pre-procedure. At the 4-month follow-up, 1 patient had died and 3 patients had angiographic evidence of restenosis (1 in-stent and 2 in-lesion). At 9 months clinical follow-up, 3 patients had experienced 4 major adverse cardiac events (2 deaths and 1 acute MI necessitating repeat target vessel angioplasty). Twenty-five patients with in-stent restenosis were successfully treated with implantation of 1 or 2 sirolimus-eluting Bx Velocity stents in Sao Paulo, Brazil.[10] Quantitative angiographic and IVUS follow-up was performed at 4 and 12 months. All vessels were patent at the time of 12-month angiography. Angiographic late loss averaged 0.07 ± 0.2 mm in-stent and -0.05 ± 0.3 mm in-lesion at 4 months, and 0.36 ± -0.46 mm in-stent and 0.16 ± -0.42 mm in-lesion after 12 months. No patient had in-stent or stent margin restenosis at 4 months and only one patient developed in-stent restenosis at 1-year follow-up. Percent volume obstruction by 3-dimensional IVUS was 0.81 ± 1.7% at 4 months and 1.76 ± 3.4% after 1 year. There were no deaths, stent thromboses, or repeat revascularizations reported.

RESEARCH Registry

The impact of the implantation of sirolumus-eluting stents on the occurrence of early adverse events (30 days) in a consecutive series of unselected "real-world" patients was evaluated in the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) registry. A total of 508 patients were enrolled in the RESEARCH registry over a 6-month period. Additionally, a control group was formed by all patients treated with percutaneous interventions in the 6-month period immediately before this study. Therefore, the control and the RESEARCH groups were constituted by 2 sequential cohorts, primarily defined by the interventional strategy applied (conventional bare stent or sirolimus-eluting stent implantation, respectively). The post-procedural antiplatelet regimen consisted of lifelong aspirin and clopidogrel 75 mg/day for 3 months in patients treated with sirolimus-eluting stents. Prolonged clopidogrel prescription (6 months) was recommended for patients treated with sirloimus-eluting stents and at least 1 of the following characteristics: multiple drug-eluting stents (>3 stents), total stented length >36 mm, chronic total occlusion, bifurcations, and in-stent restenosis. The 30-day incidence of MACE (death, nonfatal MI, or re-intervention) in those patients with unstable angina or acute MI treated with sirolimus-eluting stents (198 consecutive patients) have been reported.[11] Compared with control patients, patients treated with sirolimus-eluting stents had more bifurcation stenting (16% vs. 8%; $P < 0.01$), less previous MI (30% vs. 40%; $P < 0.01$), and less glycoprotein IIb/IIIa inhibitor utilization (19% vs. 33%; $P < 0.01$). The 30-day MACE rate was similar between both groups (sirolimus 3.0% vs. control patients 4.2%; $P = 0.3$), with most complications occurring during the first week. Stent thrombosis occurred in 0.4% of patients treated with drug-eluting stents and in 1.6% of control patients ($P = 0.4$). The one-year cumulative risk of MACE was significantly reduced in the sirolumus-eluting stent group (9.7 versus 14.8%, hazard ratio 0.62 [95% CI, 0.44-0.89]; P=0.008). The results of the RESEARCH registry indicated that sirolimus-eluting stent implantation in "real-world" patients is safe and effective in reducing both repeat revascularization and major adverse cardiac events at one year compared to bare stent implantation.

Clinical trials with paclitaxel-eluting stents

Paclitaxel (Taxol) is a potent antiproliferative agent that stabilizes the intracellular microtubules thereby inhibiting cell replication, motility, shape, and intracellular transport. Cook stents (V-Flex-Plus, Logic PTX, Supra G; Cook Inc., Bloomington, IN, USA), coated with paclitaxel using a proprietary polymer-free technology, have been examined in several clinical trials.

ELUTES

The ELUTES (European Evaluation of Paclitaxel Eluting Stent) trial examined the safety, efficacy, and dosing of paclitaxel-coated V-Flex Plus stents (V-Flex Plus PTX).[12] One hundred and ninety-two patients were divided into 5 groups; 4 groups received a 16 mm long V-Flex Plus PTX stent at 4 different doses of paclitaxel (0.2 $\mu g/mm^3$, 0.7 $\mu g/mm^3$, 1.4 $\mu g/mm^3$, 2.7 $\mu g/mm^3$) and the fifth received a non-coated stent as control. All patients had a single, *de novo* lesion in one artery. The primary endpoint of the study was effectiveness, assessed by the per cent diameter stenosis and late loss at 6 months follow-up after implantation. Safety was determined by assessing major adverse cardiac events at 1 and 6 months. The high-dose paclitaxel group showed significant reduction in diameter stenosis (14% vs 34% [$P<0.01$]). Although there was no difference between the treated groups in terms of benefit, a dose response curve was seen. Late loss was also significantly lower in the high-dose group compared to controls (0.10 mm vs. 0.73 mm, $P<0.005$), with no difference between treated groups. Only 3% of high-dose patients versus 31% of controls experienced binary in-stent restenosis (>50% diameter stenosis, $P=0.055$). There were no significant adverse events at 1 month, with a nearly 100% event-free rate in all arms. At 6 months event rates were still low among all treated groups, with between 89% and 97% of patients remaining event-free. Based on the results of the ELUTES trial, Cook Inc. received CE Mark approval to market its paclitaxel-coated V-Flex™ Plus PTX Coronary Stent System in the European Union.

A Belgian group has shown that V-Flex Plus PTX stents (Cook) are also effective for the prevention of recurrent in-stent restenosis.[13] In their study, 21 patients who had been treated a minimum of 4 times for recurring in-stent restenosis received a 16-mm Cook V-Flex Plus PTX coronary stent coated with a cytostatic dose of paclitaxel. After 6 months, no patient in the study exhibited restenosis in the portion of the target vessel where the paclitaxel-coated stent was placed.

ASPECT

The double-blind ASPECT (Asian Paclitaxel-Coated Stent Clinical Trial) randomized 177 patients to control or 1 of 2 paclitaxel dose groups, high dose (3.1 $\mu g/mm^3$), and low dose (1.3 $\mu g/mm^3$) delivered using Cook's coated Supra-G stent system, that implements a polymer-free technology to that of the V-Flex Plus PTX.[14] At 6-month follow-up, a significant dose-dependent reduction in binary restenosis rates (high dose; 4%, low dose; 12%, control; 27%) and late loss (high dose; 0.29 ± 0.72 mm, low dose; 0.57 ± 0.71 mm, control; 1.04 ± 0.83 mm) were seen in the paclitaxel arms, compared to the control group. In ASPECT, enrollees treated with conventional antiplatelet therapy (aspirin and a thienopyridine), no thrombotic complications were noted following stent implantation. In a breech of protocol, however, 37 patients were treated with aspirin and cilostazol rather than a thienopyridine following stenting. Of this group, there were thrombotic complications in 3 of the 12 patients who received a high-dose stent, 1 of the 15 patients who received a low-dose stent, and none of the 10 patients who received a bare stent. These results indicate that locally-delivered paclitaxel exhibits an important anti-restenotic effect, but likely delays wound healing in a manner that may increase the risk of stent thrombosis unless conventional antiplatelet therapy is prescribed.

DELIVER I and II

Under a partnership agreement, Cook Inc. and Guidant Corp. have developed the paclitaxel-coated Achieve stent using the Cook proprietary polymer-free coating technology on a Guidant Multilink coronary stent platform. The efficacy of the Achieve device, coated with 3 μg/mm^2 of paclitaxel, was tested in the DELIVER-I (The RX Achieve Drug-Eluting Coronary Stent System in the Treatment of Patients With *De Novo* Native Coronary Lesions-I) Trial. In this prospective, randomized, single-blind, multicentre trial, 1043 patients were enrolled at 61 US centres. The primary endpoint of a 40% reduction in target vessel failure at 270 days for the Achieve drug-eluting stent compared to the Penta stent was not met in the DELIVER-I trial.

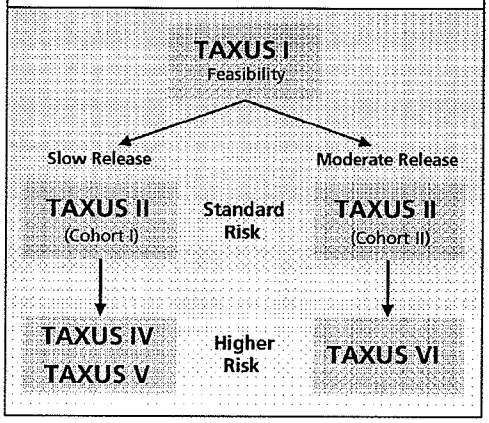
The DELIVER-II clinical study was a prospective, nonrandomized, multicentre study designed to evaluate the benefit of the Achieve drug-eluting stent in patients with complex coronary lesions with a high risk of revascularization. The study enrolled 1533 patients at 86 sites in Europe, the Middle East, and South Africa. All patients received the Achieve stent platform. The primary endpoint of the study was to elucidate the rate of target lesion revascularization (TLR) at 6 months and to identify the factors that led to an increased relative risk of revascularization in patients with complex lesions such as long lesions, small vessels, multi-vessels, chronic total/subtotal occlusions, bifurcations, or restenotic (including in-stent restenosis) lesions treated with a non-polymeric paclitaxel eluting stent. Secondary endpoints included 6-month target vessel failure and MACE rates at 30 days, 6 months, and 1 year (in a subset of 500 patients).

At 6 months, the TVR rate in the overall population was 10.5% and the hierarchical MACE rate (death, Q-wave MI, non-Q-wave MI and TVR) was 15.7%. Univariate analysis identified a history of angina and the number of diseased vessels as risk factors for worsened prognosis at 6 months. The specific characteristics identified as risk factors for TLR by multivariate analysis included:

- lesions in the left anterior descending (LAD) artery
- restenotic lesions
- post-procedural minimal lumen diameter
- total stent length
- number of diseased vessels ($P<0.05$).

The only conclusions that could be made from the results of DELIVER II were that the TLR rate in the high-risk population was low and that a number of multivariate patient/lesion risk factors contributed to the increased risk of TLR. As the study was not randomized, efficacy of the Achieve device could not be evaluated. However, based on the results of the DELIVER-I trial, questions were raised concerning the durability of the coating and how much drug was actually delivered. Early loss of paclitaxel may have occurred during insertion, or there may have been variability in dose from stent to stent. Based on the disappointing results of the DELIVER-I trial, it was decided that the Achieve stent would not be further developed.

Figure 1: Scheme outlining the Boston Scientific TAXUS paclitaxel-eluting stent clinical trials.



The TAXUS Program

The TAXUS program, which began in 1997, is a series of clinical studies being performed by Boston Scientific (Natick, MA, USA) to collect data on their proprietary paclitaxel-eluting stent technology on 2 of its stent platforms: the NIR stent (NIRx) and the Express stent (TAXUS stents) (Figure 1). The devices employed by Boston Scientific differ from those developed by Guidant/Cook in that Boston Scientific uses a polymer coating to hold and release the drug, while the Cook system involves application to the stent without a polymeric coating.

The TAXUS-I study was a prospective, randomized, double-blind, clinical trial designed to evaluate the feasibility and safety of low-dose paclitaxel-eluting stents (NIRx) used for the treatment of *de novo* and restenotic lesions.[15] The coated stents were seven cell, 15 mm long NIR stents containing 1 μg paclitaxel/mm^2 (85 μg/stent) and uncoated NIR stents served as controls. The trial was performed at 3 centres in Germany and included 61 patients. The primary endpoint was the incidence of MACE at 30 days. There were no adverse events reported in either group at 30 days and no stent thromboses were reported up to 12 months. The 6-month binary restenosis rate (>50% diameter stenosis) was 10% in the bare control stent group compared with "zero" restenosis in the paclitaxel-coated stent group (P=NS). At 12 months, the MACE rate was 3% in the paclitaxel treated group and 10% in the control group (P=NS).

TAXUS II was a 536-patient, 15-country, randomized, double-blind, controlled study of the safety and efficacy of the NIRx paclitaxel-eluting coronary stent, in which 2 sequential cohorts of patients with standard risk, *de novo* coronary artery lesions were treated with different dose formulations. The primary endpoint of the trial was

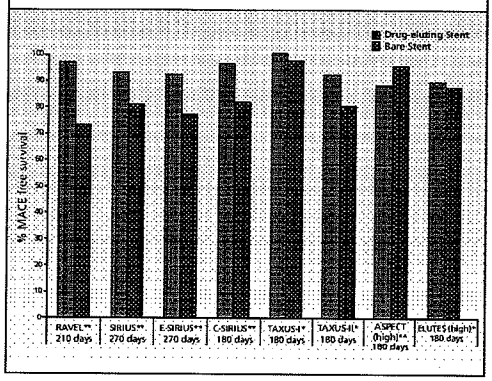
the reduction of mean percent in-stent net volume obstruction at 6 months as measured by IVUS. The slow-release formulation (NIRx SR stent, 1 μg/mm²) cohort showed a significant 66% reduction in in-stent volume obstruction as measured by IVUS at 6-month follow-up (7.9% vs 23.2%, NIRx SR stent vs control, P<0.0001). The slow-release cohort reported an 8.5% MACE rate at 6 months compared with 19.5% in the control group (P=0.013). Binary restenosis rates were 2.3% for the NIRx SR group compared with 17.9% in the control group (P<0.0002). The moderate-release formulation (NIRx MR stent, 1 μg/mm²) cohort reported a significant 62% reduction in in-stent volume obstruction at 6-month follow-up (7.8% vs 20.5%, NIRx SR stent vs control, P<0.0001). The moderate-release cohort reported a 7.8% MACE rate at 6 months compared with 20.0% in the control group (P=0.006). Binary restenosis rates were 4.7% for the NIRx MR group compared with 20.2% in the control group (P<0.0001).

TAXUS III was a single-arm, 28-patient registry study that examined the feasibility and safety of the paclitaxel slow-release formulation on a NIRx platform for treatment of in-stent restenosis. No subacute stent thrombosis occurred up to 12 months, but there was one late chronic total occlusion and an additional 3 patients showed angiographic restenosis.[16] The mean late loss was 0.54 mm. The MACE rate was 29%.

The TAXUS IV trial was a prospective, randomized, double-blind study designed to assess the safety and efficacy of a slow-release dose formulation paclitaxel-eluting TAXUS Express stent system in patients with a single *de novo* lesion up to 28 mm long and 3.75 mm in diameter amenable to treatment with a single stent. A total of 1326 patients were randomized, with a primary endpoint of TVR at 9 months. Treatment with clopidogrel was given for 6 months post-procedure. At 9 months, the TVR rate in the control stent group was 12.0% compared with 4.7% in those treated with paclitaxel-eluting stents (P<0.0001). Sub-group analysis revealed that the devices were equally effective for the reduction in restenosis rates in diabetics treated with oral hypoglycemic medications (TLR rates of 17.4% in patients receiving a bare stainless-steel stent compared with 4.8% in those treated with a TAXUS drug-eluting stent, P = 0.004); however, a similar benefit was not documented in insulin-treated diabetic patients (TLR rate of 13% in control patients compared with 5.9% in those receiving a paclitaxel-eluting stent. The results of TAXUS-IV support the effectiveness of the slow-release paclitaxel-eluting TAXUS stent for the reduction of restenosis in a wide range of complex patients and lesions, including small vessels, long lesions, and patients with diabetes.

The TAXUS V trial is an extension of TAXUS IV, and it is studying higher risk patients, including those with smaller vessels, as well as those with longer lesions requiring overlapping stents. TAXUS V is currently underway with a planned enrollment of 1108 patients.

Figure 2: Major adverse clinical events (MACE)-free survival (MACE) of the various drug-eluting stent trials at < 1 year.



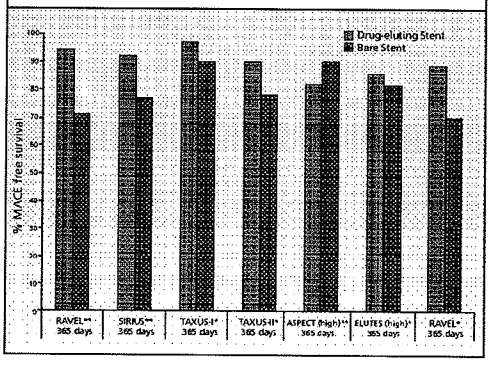
* MACE includes target lesion revascularization for all reasons.
** MACE includes only clinically driven target lesion revascularization.

TAXUS VI is a prospective, randomized, double-blind trial studying the efficacy of the implantation of a moderate-release paclitaxel-eluting stent in patients with long lesions. Inclusion criteria in this trial included single or sequential lesions which could be completely covered by up to two study stents (maximum stent length 48 mm). The planned enrollment of 448 patients is complete and final results will soon be available.

The main results of the drug-eluting stent trials are shown in Figures 2, 3, and 4.

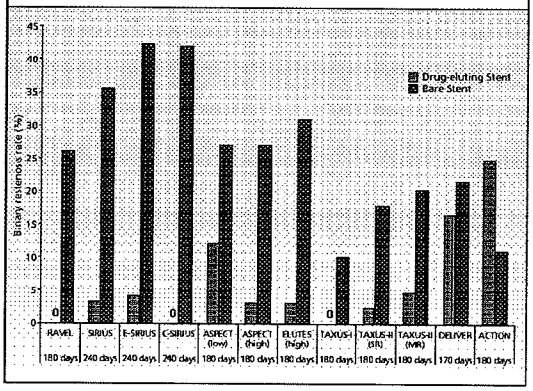
In the December issue of *Cardiology Rounds*, this review of clinical trials of drug-eluting stents continues with the examination of QP-2, actinomycin D, phosphorylcholine, everolimus, and 17ß-estradiol loaded BiodivYsio Matrix LO–eluting stents, as well as a review of biodegradable stents. Thoughts on the future of this rapidly evolving treatment and new approaches for its use in the treatment of coronary artery disease will also be discussed.

Figure 3: MACE-free survival of the various drug-eluting stent trials at ≥ 1 year.



* MACE includes target lesion revascularization for all reasons.
** MACE includes only clinically driven target lesion revascularization.

Figure 4: In-stent binary restenosis rates (>50% diameter stenosis as measured by quantitative coronary angiography) of the major drug-eluting stent trials.



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AS PRESENTED IN THE ROUNDS OF THE DIVISION OF CARDIOLOGY, ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Drug-eluting stents for the treatment of coronary artery disease Part 4: New results from clinical trials and future directions.

By MICHAEL J. B. KUTRYK, MD, PhD, FRCPC

The implantation of drug-eluting stents has become the percutaneous treatment of choice for many patients with coronary lesions. In 2002, two issues of *Cardiology Rounds* reviewed the development and early trials of drug-eluting stents for the treatment of coronary artery disease. Because several important new multicentre clinical trials with updated information have been published over the past year, the aim of both the November and December 2003 issues of *Cardiology Rounds* is to provide an update for our readers. The November issue summarized data from trials with sirolimus-eluting stents (FIM, RAVEL, SIRIUS, and the RESEARCH registry) and paclitaxel-eluting stents (ELUTES, ASPECT, DELIVER I and II, and TAXUS I-V). Part 4, in this issue, continues with an examination of QP-2, actinomycin D, phosphorylcholine, everolimus, and 17ß-estradiol loaded BiodivYsio Matrix LO–eluting stents. Future directions for this rapidly evolving treatment are also discussed.

Clinical trials with QP2 (7-hexanoyltaxol)-eluting stents

7-hexanoyltaxol, (QP2), a taxane, has been tested on a unique stent delivery platform for the prevention of restenosis. QP2 is a more hydrophobic derivative of paclitaxel that causes similar disruptions of the cell cycle by inhibition of microtubule formation. The efficacy of QP2 for the inhibition of restenosis when delivered locally on a stent platform has been tested using the QuaDDS-QP2 stent (Boston Scientific Corporation Inc./Quanam Medical, Santa Clara, California, U.S.A.). The QuaDDS-QP2 stent was based on the uncoated QueST stent platform (Quanam Medical Corporation). The QueST stent is a laser cut, stainless steel, tubular stent. The QuaDDS stent is a QueST stent covered with a series of 2 mm wide, rigid polymer sleeves that are approximately 0.0025 inches (0.06 mm) thick and placed equidistant from each other over the length of the stent. The non-biodegradable proprietary polymer sleeve is loaded with QP2 by dissolving the drug in a solvent that absorbs into and swells the polymer; the solvent is then removed by vacuum drying. The total dose per sleeve is approximately 800 µg of QP2; the 13 mm stent (4 sleeves) carries 3.2 mg and the 17 mm stent (5 sleeves) carries 4.0 mg of QP2.

In the first clinical study of the QuaDDS-QP2 stent, 14 QuaDDS-QP2 stents were implanted in 13 patients and 18 control bare QueST stents were implanted in 14 patients.[1,2] Both 13 mm and 17 mm stents were used. After 18 months, the binary restenosis rate (>50% diameter stenosis) in the coated-stent group was 0% as compared to 54% in the control group. The incidence of major adverse cardiac events (MACE) after 18 months was 0% in the drug-eluting stent group and 15% in the control group. Two-year follow-up data showed no binary restenosis and a target lesion revascularization (TLR) rate of 0. Intravascular ultrasound (IVUS) analysis revealed only minimal neointimal proliferation.[2]

Based on the promising results of this pilot study, the phase II, the SCORE (Study to Compare Restenosis Rate Between QueST and QuaDDS-QP2) trial was initiated. The primary endpoint of this randomized, multicentre trial was target vessel revascularization (TVR) with an anticipated reduction in restenosis rate to <20% as compared to a rate of 24% to 42% seen with traditional stainless steel

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stents. Four hundred patients from 17 centres in Europe and Australia were to be enrolled in this trial; only patients with *de novo* lesions were included. Implanted QuaDDS-QP2 stents were either 13 or 17 mm in length and the target lesion had to be suitable for stenting with a single stent. Interim analysis of safety outcomes, however, led to the termination of the SCORE trial. At the time of termination, 266 patients were enrolled. There was no stent thrombosis seen in the control group and a 5.5% stent thrombosis rate was present in the QuaDDS-QP2 group. There was also an increase in periprocedural myocardial infarctions (MIs) that were usually related to side-branch occlusion caused by the polymer bands. MACE at 30 days in the treated group was 10.2%, predominantly due to subacute stent thrombosis and MI. Further development of the QuaDDS-QP2 stent has been suspended.

Clinical studies with actinomycin D

In preclinical studies, the Multilink tetra-D stent (Guidant), coated with a T.R.U.E. Coat™ (Targeted Release Uniform Elution) polymer containing actinomycin D, demonstrated significant inhibition of neointimal proliferation and complete re-endothelialization of the treated site at the 30-day time point with the 2.5 μg/cm² and 10 μg/cm² doses. Actinomycin D functions by binding DNA in all phases of cell cycle proliferation, thereby preventing cell division and protein production.

The ACTION (Actinomycin Eluting Stent Improves Outcomes by Reducing Neointimal Hyperplasia) trial was a randomized, single-blind, clinical trial designed to evaluate the safety and performance of the Multilink tetra-D actinomycin-D-eluting stent system. A total of 360 patients at 28 clinical sites in Europe, Brazil, Australia, and New Zealand were randomized to 3 arms and received either a high-dose (10 μg/cm²) or low-dose (2.5 μg/cm²) actinomycin-D-coated or non-coated stent. Clinical follow-up was planned for 30 days, and 6 and 12 months, with angiographic follow-up at 6 months. The ACTION study was completed, but the Safety Committee directed that the randomization code be prematurely broken and follow-up accelerated due to a higher incidence of restenosis in patients treated with the actinomycin-D-eluting stent. Quantitative angiography (QCA) at 6 months demonstrated greater late loss in the drug-eluting stent arms (0.76 mm, control vs 1.01 mm, low-dose vs 0.93 mm, high-dose; $p<0.05$). In addition, binary restenosis rates were significantly higher in the low-dose drug treatment arms compared to bare stent (25% vs 11%; $p<0.05$). Proximal and distal edge restenosis was also more common in the drug-eluting stent arms. While no significant increases in death or MI were found, TLR was dramatically higher in the drug-eluting stent arms (17.5% low-dose and 23.1% high-dose vs 9.1% control) leading to a significant difference in the combined primary endpoint (18.3 % low-dose, 28.1% high-dose, 10.2% control; $p<0.002$ for high-dose compared to control). Based on these discouraging results, Guidant suspended all further development of actinomycin-D-eluting stents. The evidence from the ACTION trial further illustrates that results from animal data cannot be readily generalized to human populations.

Trials using phosphorylcholine-coated stents

The phosphorylcholine technology of Abbott Vascular Devices is well-suited for stent-mediated drug delivery. The phosphorylcholine coating has the ability to absorb and release a wide range of drugs. There are 2 phosphorylcholine-coated drug delivery formats currently available: BiodivYsio Matrix LO stents and BiodivYsio Matrix HI stents.

- The BiodivYsio Matrix LO stents were designed specifically for water-soluble drugs with a molecular weight of <1200 daltons.
- The BiodivYsio Matrix HI stent was designed for interaction with negatively-charged components (eg, DNA, heparin, and oligonucleotides) and will easily adsorb and deliver compounds with molecular weights >1200 daltons.

The use of BiodivYsio Matrix systems has been shown to be effective in preventing restenosis in a number of pre-clinical studies. Animal studies have been performed using a range of drugs that include angiopeptin,[3] dexamethasone, methylprednisolone, the matrix metalloprotease inhibitor Batimastat, radioactive antisense oligonucleotides,[4] 17ß-estradiol,[5] and Resten-NG[6] (AVI-4126, AVI BioPharma, Inc.) an advanced 6-ring morpholino backbone neutrally charged c-myc antisense compound.[6]

The STRIDE (Study of Anti-Restenosis with BiodivYsio Matrix LO Dexamethasone-Eluting Stent) study was a multicentre prospective registry series. The study objectives were to evaluate the safety and efficacy of the BiodivYsio Matrix LO stent with dexamethasone (Dexamet stent). Dexamethasone is an anti-inflammatory corticosteroid that is used to inhibit the inflammatory response and reduce tissue injury due to trauma. The rationale behind the development of the Dexamet stent was that delivery of dexamethasone to the site of injury could prove beneficial through the inhibition of cytokines and lead to a reduction in inflammatory cell proliferation around the stent struts, with a resultant reduction in restenosis. Seventy-one patients at 8 sites in Belgium were recruited into the STRIDE study. It demonstrated that implantation of a phosphorylcholine-coated coronary stent coated with dexamethasone (0.5 μg/mm²) resulted in a 52.1% improvement in late lumen loss (0.45mm) and an 80.6% reduction in the occurrence of MACE (3.3%) at 6-month follow-up when compared to the results of the earlier DISTINCT trial that evaluated phosphorylcholine-coated stents without a drug coating. The results of the STRIDE trial were used to obtain CE-mark approval in Europe for the Dexamet stent.

The antimigratory compound Batimastat was tested on the BiodivYsio Matrix drug-eluting stent system in a number of clinical trials. Batimastat is a broad-spectrum matrix metalloproteinase inhibitor (MMPI) developed by British Biotech, the UK bio-pharmaceutical company. It is a low-molecular weight peptide mimetic containing a hydroxamate group that chelates the zinc atom in the active site of the MMP, thereby inhibiting the enzyme. Batimastat is a potent, but reversible, inhibitor of the MMPs and displays IC50s in the low nanomolar range against all 3 classes of MMPs: collagenases, stromelysins, and gelatinases (alternatively referred to as type IV collagenases). Collectively, these enzymes can degrade all

the components of the extracellular matrix and induce cell migration and proliferation. The injury to the vessel wall caused by a stent and the resulting smooth muscle cell proliferation causes expression of several members of the MMP family. Batimastat can inhibit the cell migration and proliferation process.

The **BRILLIANT-I** [Batimastat (BB-94] Antirestenosis Trial utilizing the BiodivYsio Local Drug Delivery PC Stent) study was a 173-patient safety trial that included patients from 24 clinical sites in France, Belgium, and the Netherlands, and was designed to evaluate the safety and efficacy of the Batimastat-eluting BiodivYsio Matrix stent. Six-month angiographic and clinical follow-up on an initial group of patients from BRILLIANT I indicated that there was no evidence of benefit with the Batimastat BiodivYsio stent in pre-clinical studies, demonstrating a 6-month binary restenosis rate of 21% and a total MACE rate of 18%. Based on the discouraging results of the BRILLIANT-I trial, enrollment of patients into the double-blind, randomized BRILLIANT-II clinical trial was halted and further development of the Batimastat-eluting stent was suspended.

The **EASTER** (Estrogen and Stents to Eliminate Restenosis) pilot trial was designed to evaluate the safety of 17ß-estradiol loaded BiodivYsio Matrix LO stent system in treating *de novo* coronary artery lesions. The study was a 30-patient, single-site, registry series with 6-month angiographic and IVUS follow-up. The primary endpoint was safety and late loss at 6 months. The average 17ß-estradiol dose released from the stent was 2.54 µg/mm^2. At 6-month follow-up, there were no reported deaths or MIs. There was a 3.3% rate of TLR and the event-free survival was 93.4%. Late loss at 6-month follow-up was 0.54 ± 0.44 mm. The 200-patient, 5-site, prospective, randomized EASTER trial has been completed and results will soon be released.

A summary of the on-going and completed drug-eluting stent trials is shown in Table 1.

Everolimus-eluting stent

The **FUTURE I** clinical trial was a prospective, randomized, single-blind trial evaluating the safety of an everolimus-eluting stent utilizing an ultra-thin, resorbable polymer drug-delivery coating vs a bare metal stent platform in *de novo* lesions. Everolimus, a rapamycin analogue previously studied for organ transplant applications, also exerts its immunosuppressant effect by inhibiting the mammalian target of rapamycin (mTOR). Eleven patients were treated with a control metallic stent (S-Stent; Biosensors International, Singapore) and 25 patients received an everolimus-eluting S-Stent (Challenge stent). Six-month angiographic follow-up analyses demonstrated a significant reduction in angiographic late loss (0.1 mm in the everolimus-eluting stent group compared to 0.83 mm in the control arm). IVUS follow-up demonstrated that patients who received the everolimus-eluting stent had a statistically significant reduction in the percent of neointimal volume compared to the control group. No angiographic in-stent binary restenosis was observed in the everolimus-treated arm. Both the safety and efficacy results from FUTURE I at 6 months were sustained at the 12-month follow-up. Twenty-four patients who had received the everolimus-eluting stent were evaluated at 12 months. No new MACE occurred between 6 and 12 months, with no incidence of repeat intervention required. Preliminary angiographic analysis of 8 patients showed no new binary restenosis events. In 6 patients who underwent follow-up IVUS, the results were consistent with 6-month results, demonstrating minimal re-narrowing of the artery (luminal volume obstruction).

Results reported from the 6-month follow-up of **FUTURE II**, a prospective, randomized, multicentre, double-blind trial that included 64 patients (21 receiving the Challenge stent and 43 receiving a bare metal device) confirmed the 6-month results of the FUTURE I trial. FUTURE II, which included a more complex patient group than FUTURE I, reported a 4.8% rate for MACE in the everolimus-eluting stent arm at 6 months. Angiographic endpoint results were positive, with 0% in-stent restenosis in the everolimus arm vs 19.4 % in the control arm.

Guidant has acquired Biosensors' drug-eluting stent technology and is applying everolimus to its own proprietary eluting stent system. **VISION-E** is a two-phase trial that will be conducted outside the U.S. Phase 1 is a dose-ranging study that will include 3 arms using different concentrations of everolimus in Guidant's proprietary polymer coating on Guidant's Vision cobalt chromium stent, and a fourth control arm. The study will be conducted at 15 sites and will enroll a total of 140 patients. Phase 2 of this study will continue with the everolimus concentration that demonstrated the best result in phase 1 and will enroll 150 patients.

Tacrolimus-eluting stents

The results of the **PRESENT** (Preliminary Safety Evaluation of Nanoporous Tacrolimus Eluting Stents) and **EVIDENT** (Endo-Vascular Investigation Determining the Safety of a New Tacrolimus Eluting Stent Graft) clinical studies examining the effectiveness of tacrolimus in native coronary arteries and saphenous vein grafts have recently been released. Structurally, tacrolimus resembles sirolimus and binds to the same intracellular binding protein or immunophilin (FKBP-12). Unlike sirolimus, tacrolimus does not block the activation of mTOR.

The **PRESENT I** safety study tested a Jomed FlexMaster low-dose (60 µg tacrolimus) tacrolimus-eluting stent employing Jomed's proprietary nanoporous ceramic layer of aluminum oxide as the delivery platform. The PRESENT I study was halted after the enrollment of 22 patients into the treatment group. There were no MACE reported at 30 days (primary endpoint); however, the 6-month MACE rate was 13.6% in the treatment group. Late loss in the treated group was 0.81 mm and the binary restenosis rate was 19%. The **PRESENT II** registry study tested a high-dose (230 µg) tacrolimus-eluting stent and enrolled 30 patients. The primary endpoint, MACE at 30 days, was 0, but at 6 months, MACE was 32.0% in the tacrolimus-treated group.

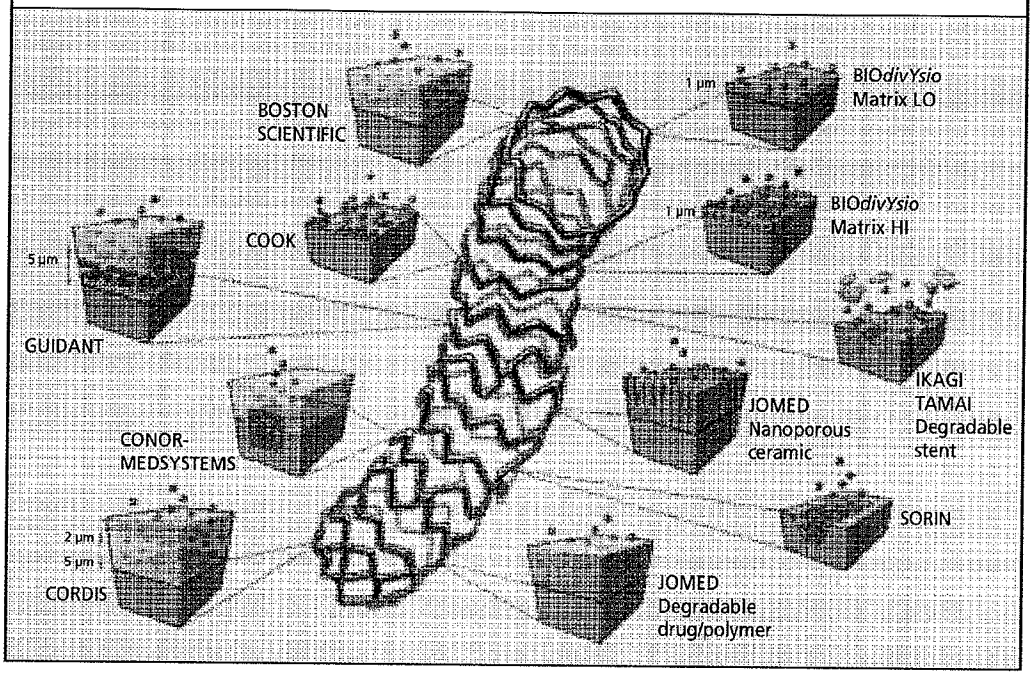
The **EVIDENT** registry study enrolled 20 patients and was designed to examine the safety of the implantation of tacrolimus (325 mg) eluting, ePTFE-covered, Jomed stents in *de novo* saphenous vein graft lesions. The 30-day MACE rate

Table 1: Ongoing and completed drug-eluting stent trials

Trial Name (Company)	Stent	# of Patients	Lesion Type	Design
RAPAMYCIN, SIROLIMUS				
RAVEL (Cordis/J&J)	CYPHER vs Bx Velocity	238	*De novo* lesions	Efficacy of rapamycin eluting stents (Europe and Latin America) PRDBC study; PE: Late loss at 6 months
SIRIUS (Cordis/J&J)	CYPHER vs Bx Velocity	1101	*De novo* lesions	Efficacy of rapamycin eluting stents (U.S.A.); PRDBC study PE: 9 month target lesion failure
E-SIRIUS (Cordis/J&J)	Bx Velocity	350	*De novo* lesions	Efficacy of rapamycin eluting stents (Europe and Latin America) PRDBC study; PE: 9 month target lesion failure
FIM (Cordis/J&J)	Slow release vs fast release Bx Velocity	45	*De novo* lesions	Safety of fast- and slow-release rapamycin eluting stents Registry; PE: Safety and efficacy
ISR (Cordis/J&J)	Bx Velocity	41	In-stent restenosis	Safety of rapamycin eluting stents for in-stent restenosis Registry; PE: Safety and efficacy
BIFURCATION (Cordis/J&J)	Bx Velocity	21	*De novo* bifurcation lesions	Safety of rapamycin eluting stents for in-stent restenosis Registry; PE: Safety and efficacy
FREEDOM (Cordis/J&J)	Bx Velocity	1500	*De novo* lesions in diabetics	CABG vs multi-vessel stenting with rapamycin eluting stents in diabetics; PRC study; PE: MACE at 1 year
RESEARCH (Cordis/J&J)	Bx Velocity	563	"Real world"	Efficacy of rapamycin eluting stents in "real world" lesions, consecutive patients; Registry; PE: Safety and Efficacy
PACLITAXEL, TAXOL				
TAXUS I (BS)	Slow release NIR vs bare NIR	61	*De novo* lesions	Safety and feasibility of implantation of paclitaxel eluting stents PRDBC study; PE: 30 day MACE
TAXUS II (BS)	Slow release and moderate release vs bare NIR	536	*De novo* lesions	Efficacy of paclitaxel eluting stents, slow release vs. bare and moderate release vs. bare PRDBC study; PE: Plaque volume by IVUS at 6 months
TAXUS III (BS)	Drug-eluting NIR	30	In-stent restenosis	Safety and feasibility of implantation of paclitaxel eluting stents for instent restenosis; Registry series PE: 30 day MACE and 6-month angiographic and IVUS follow-up
TAXUS IV (BS)	Slow release Express vs bare Express	1326	*De novo* lesions	Efficacy of paclitaxel eluting stents in *de novo* lesions up to 28 mm long and 3.75 mm in diameter using a slow release formulation; PRDBC; PE: 9 month follow up
TAXUS V (BS)	Slow release Express vs bare Express	1512	*De novo* long lesions and small diameter lesions, In-stent restenosis	Efficacy of paclitaxel eluting vs bare stents in *de novo* lesions up to 44 mm in length and as small as 2.25 mm in diameter, paclitaxel eluting stents vs brachytherapy in pts with ISR PRDBC/PRC; PE: 9 month target vessel revascularization
TAXUS VI (BS)	Moderate release Express vs bare Express	448	*De novo* long lesions	Efficacy of moderate-release paclitaxel eluting stents in long lesions (≥18 mm,≤40 mm) PRDBC; PE: 9 month target vessel revascularization
ELUTES (Cook)	V-Flex Plus	192	*De novo* lesions	Safety and efficacy of paclitaxel coated stents using four doses compared to bare PRDBC; PE: % diameter stenosis and late loss at 6 months
DELIVER (Cook/GDT)	Achieve stent vs bare Penta stent	1043	*De novo* lesions	Efficacy of paclitaxel eluting stents for *de novo* lesions PRDBC; PE: target vessel failure at 9 months
DELIVER II (Cook/GDT)	Achieve stent vs bare Penta	1533	*De novo* lesions	Efficacy of paclitaxel eluting stents for lesions at high risk for restenosis; PRDBC; PE: target vessel revascularization at 6 months
ASPECT (Cook)	Supra-G	177	*De novo* lesions	2 arms of 57 patients testing different doses of paclitaxel and control bare stent; PRDBC; PE: 6 month binary restenosis rate
ACTINOMYCIN D				
ACTION (GDT)	Drug eluting MULTI-LINK vs bare	360	*De novo* lesions	Efficacy of Actinomycin D eluting stents using 2 doses compared to bare; PRDBC; TRIAL TERMINATED MARCH 2002
7-HEXANOYLTAXOL				
SCORE (BS/Quanum)	QueST stent vs bare stent	400	*De novo* lesions	Efficacy of 7-hexanoyltaxol coated stents; PRDBC TRIAL TERMINATED AFTER ENROLLMENT OF 266 PATIENTS
DEXAMETHASONE				
STRIDE (Biocompatibles)	BiodivYsio	71	*De novo* lesions	Safety and feasibility of implantation of dexamethasone eluting stents; Registry; PE: Safety
BATIMASTAT				
BRILLIANT I (Biocompatibles)	BiodivYsio	150	*De novo* lesions	Safety and feasibility of implantation of Batimastat eluting stents Registry; PE: Safety
BRILLIANT II (Biocompatibles)	BiodivYsio	400	*De novo* lesions	Safety and feasibility of Batimastat eluting stents PRDBC; TRIAL TERMINATED
TACROLIMUS				
EVIDENT (Jomed)	JoStent Stent Graft	30	*De novo* lesions in saphenous vein grafts	Safety and feasibility of tacrolimus eluting stent graft in SVGs Registry series; PE: 30 day MACE
PRESENT I (Jomed)	Ceramic Flexmaster (low dose)	22	*De novo* lesions	Safety and efficacy of tacrolimus eluting ceramic coated stents compared with control; Registry series; TRIAL HALTED
PRESENT II (Jomed)	Ceramic Flexmaster (high dose)	30	*De novo* lesions	Safety and efficacy of tacrolimus eluting ceramic coated stents compared with control; Registry series; PE: 30 day MACE
EVEROLIMUS				
FUTURE (Biosensors)	Challenge stent	36	*De novo* lesions	Safety and efficacy of everolimus eluting stents compared with control; PRSBC; PE: Safety and 6 month restenosis
17-BETA ESTRADIOL				
EASTER (BiodivYsio)	BiodivYsio Matrix LO	30	*De novo* lesions	Safety and efficacy of 17b-Estradiol loaded stents Registry series; PE: Safety and late loss at 6 months

J&J = Johnson and Johnson, BS = Boston Scientific, GDT = Guidant,
PRDBC = Prospective randomized double-blind controlled, PRC = prospective randomized controlled,
PRSBC = Prospective randomized single-blind controlled, PE = Primary endpoint

Figure 1: Stent-mediated delivery methods



1. Boston Scientific; polystyrene-polyisobutylene polystyrene copolymer intermediate layer
2. Cook; non-polymerized albumin coating
3. Guidant; ethylene-vinyl acetate intermediate layer
4. Conor-Medsystems: polylactide/glycolide copolymer intermediate layer
5. Cordis: ethylene-vinyl acetate and poly(n-butyl methacrylate) polymer intermediate layers
6. Abbot/Jomed: ethylene-vinyl acetate intermediate layer
7. Sorin: no coating
8. Jomed: nanoporous ceramic
9. Igaki Tamai: poly-L-lactic acid stent
10. BiodivYsio Matrix LO; phosphorylcholine coating
11. BiodivYsio Matrix HI; phosphorylcholine coating.

was 0%, while the 6-month MACE rate was 36.4%. The binary restenosis rate at 6 months was 27%.

Conclusion

Two major milestones in the evolution of the subdiscipline of interventional cardiology were the development of the angioplasty balloon by Andreas Gruentzig and the introduction of the coronary artery stent. The development of the drug-eluting stent has been called the third revolution in this rapidly evolving field.[11] Although it has only been 3 years since the release of the incredible first clinical results of the First in Man (FIM) trials,[12,13] drug-eluting stents have monopolized all discussions of new stent technologies. With a few notable exceptions, outcomes from subsequent studies using different pharmacologic preparations and eluting matrices have been highly positive, although less than perfect. There is a growing faction of dissenting cardiologists who believe that drug-eluting stents are not the answer to all of the interventionalist's problems. Criticism of the indiscriminate use of drug-eluting stents as a panacea for all lesion subsets, in all clinical situations, stems from the recent results of longer-term studies in broader patient populations that show the emergence of troubling clinical issues. Cases of restenosis at the stent edges and within the body of the stent have been observed. Animal studies of drug-eluting stents have shown the presence of fibrin, inflammatory cells, incomplete endothelialization, and at 3 months, with sirolimus, when the drug has been completely eluted from the stent, neointimal growth is at levels comparable to that seen with bare stainless-steel stents. Delayed endothelialization has also been seen in human arteries treated with drug-eluting stents[14] and there is concern that as human trials provide longer-term data, late restenosis may become apparent. There is speculation that the complete inhibition of healing provided by drug-eluting stents may prevent encapsulation of the stent with resultant stent mal-apposition and possible dislodgment. Results from the RAVEL study have shown that late, incomplete, stent apposition has been detected more frequently in drug-eluting stent-treated groups, however, its occurrence has not translated into clinical adverse events at 1 year.[15]

The acceptance of drug-eluting stents has followed the same course as all newly introduced technologies.

The initial period of overblown enthusiasm has been quickly followed by a period of intellectual reproach. It is clear that for a relatively new technology, the use of drug-eluting stents has had an unprecedented impact on the practice of interventional cardiology. It is unlikely that one drug released by a single matrix on a particular stent design will show the same efficacy in all clinical situations. More biologically friendly coatings that promote, rather than inhibit, natural healing processes, are being rapidly developed. An example of such an approach is the use of immobilized antibodies to circulating endothelial progenitor cells as a means of "autoseeding" intravascular devices. Such technologies show promise for use in combination with drug-eluting stent platforms and may, in fact, provide a more physiological alternative to their use. With the development of better devices, uniquely engineered to be specific for each lesion subset, the dream of a "coup" over surgical revascularization techniques might be realized.

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